PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

# PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

| | |
|---|---|
| **Date of mailing** (day/month/year)<br>04 April 2000 (04.04.00) | |
| **International application No.**<br>PCT/GB99/02957 | **Applicant's or agent's file reference**<br>PHM70385/WO |
| **International filing date** (day/month/year)<br>07 September 1999 (07.09.99) | **Priority date** (day/month/year)<br>12 September 1998 (12.09.98) |
| **Applicant**<br>LUKE, Richard, William, Arthur et al | |

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

14 March 2000 (14.03.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

**The International Bureau of WIPO**
**34, chemin des Colombettes**
**1211 Geneva 20, Switzerland**

Facsimile No.: (41-22) 740.14.35

Authorized officer

Pascal Piriou

Telephone No.: (41-22) 338.83.38

# PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

To:

BRYANT, Tracey
AstraZeneca UK Limited
Global Intellectual Property
Alderley Park, Mereside
Macclesfield
Cheshire SK10 4TG
ROYAUME-UNI

## NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

| | |
|---|---|
| **Date of mailing** (day/month/year)<br>10 May 2000 (10.05.00) | |
| **Applicant's or agent's file reference**<br>PHM70385/WO | **IMPORTANT NOTIFICATION** |
| **International application No.**<br>PCT/GB99/02957 | **International filing date** (day/month/year)<br>07 September 1999 (07.09.99) |

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
ZENECA LIMITED
15 Stanhope Gate
London W1Y 6LN
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address
ASTRAZENECA UK LIMITED
15 Stanhope Gate
London W1Y 6LN
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

**The International Bureau of WIPO**
**34, chemin des Colombettes**
**1211 Geneva 20, Switzerland**
Facsimile No.: (41-22) 740.14.35

Authorized officer
Dominique DELMAS
Telephone No.: (41-22) 338.83.38

Copy for the Elected Office (EO/US)

PCT/GB99/0295

# PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

## PCT

### NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

BRYANT, Tracey
AstraZeneca UK Limited
Global Intellectual Property
Alderley Park, Mereside
Macclesfield
Cheshire SK10 4TG
ROYAUME-UNI



**Date of mailing** (day/month/year)
01 August 2001 (01.08.01)

**Applicant's or agent's file reference**
PHM70385/WO

**IMPORTANT NOTIFICATION**

**International application No.**
PCT/GB99/02957

**International filing date** (day/month/year)
07 September 1999 (07.09.99)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
ASTRAZENECA UK LIMITED
15 Stanhope Gate
London W1Y 6LN
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address
ASTRAZENECA AB
S-151 85 Södertälje
Sweden

State of Nationality: SE
State of Residence: SE
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:
**Assignment.**

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

**The International Bureau of WIPO**
**34, chemin des Colombettes**
**1211 Geneva 20, Switzerland**
Facsimile No.: (41-22) 740.14.35

Authorized officer
Elisabeth KÖNIG
Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| Applicant's or agent's file reference | **FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. | |
|---|---|---|
| PHM70385/WO | | |
| International application No. | International filing date *(day/month/year)* | (Earliest) Priority Date *(day/month/year)* |
| PCT/GB 99/ 02957 | 07/09/1999 | 12/09/1998 |
| Applicant | | |
| ZENECA LIMITED et al. | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   PIPERAZINE-4-PHENYL DERIVATIVES AS INHIBITORS OF THE INTERACTION BETWEEN MDM2 AND P53

5. With regard to the **abstract,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. -

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNAT L SEARCH REPORT

International application No.
CT/GB 99/02957

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 13, 15
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 13 and 15 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

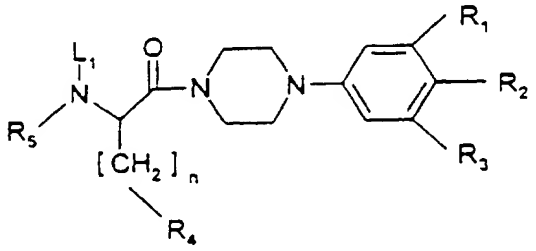
**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Box III TEXT OF THE ABSTR(C ntinuation f item 5 f the first sheet

A compound of formula (1):



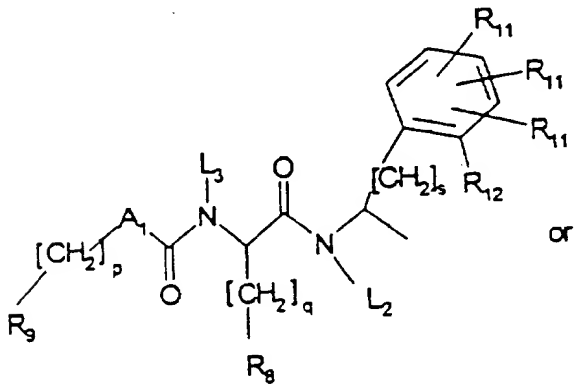
formula (1)

wherein :

$R_5$ is hydrogen, $C_{1-4}$alkyl, $R_6CH_2-$ or $R_6C(O)-$;

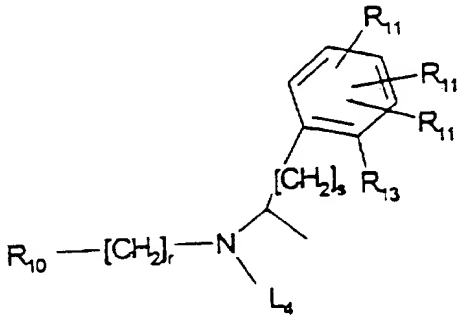
$R_6$ is aryl, heteroaryl, heterocyclyl, amino$C_{1-6}$alkyl, N-($C_{1-4}$alkyl)amino$C_{1-6}$alkyl, NN-(di$C_{1-4}$alkyl)amino$C_{1-6}$alkyl, or $R_7$; wherein the aryl, heteroaryl or heterocyclyl rings may be optionally substituted with up to three substituents independently selected from nitro, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, halo, ($C_{1-4}$alkyl)sulfanyl, $C_{1-4}$ alkoxycarbonyl, N-($C_{1-4}$ alkyl)carbamoyl, NN-(di$C_{1-4}$ alkyl)carbamoyl, N-($C_{1-4}$ alkyl)amino or NN-(di$C_{1-4}$ alkyl)amino;

wherein $R_7$ is either a group of formula (2) of formula (3):



Formula (2)

or



Formula (3)

and wherein $L_1$, $L_2$, $L_3$, $L_4$, $R_1$, $R_2$, $R_3$, $R_4$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $A_1$, n, p, q, r and s are as defined in claim 1.

The compounds of formula (1) inhibit the interactions between MDM2 and p53 and may be useful in the treatment of cancers.

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/02957

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K5/08 C07D295/185 C07D209/20 A61K38/06 A61K31/495
A61K31/496 C07D405/12 C07D409/12 C07D401/12 C07D417/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | CHEMICAL ABSTRACTS, vol. 116, no. 13, 30 March 1992 (1992-03-30) Columbus, Ohio, US; abstract no. 128656z, FURUTA TAKUYA ET AL.: "Preparation of Indole Derivatives as Vasopressin Antagonists" page 863; column 1; XP002125251 abstract -& CHEMICAL ABSTRACTS 13TH COLLECTIVE INDEX; CHEMICAL SUBSTANCES (AZAU...-BENZAMIDE, TETRAE...), vol. 116-125, 1992 - 1996, page 1647 XP002125250 Columbus, Ohio, US column 2, line 60 - line 64 & JP 03 127732 A (OTSUKA PHARMACEUTICAL) 30 May 1991 (1991-05-30) -/-- | 1,4,12, 17 |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 20 December 1999 | 19/01/2000 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016 | Zervas, B |

1

Form PCT/ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/02957

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication,where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | WO 98 01467 A (NOVARTIS)<br>15 January 1998 (1998-01-15)<br>cited in the application<br>claims; examples | 1,12,14,<br>16 |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 99/02957

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 9801467 A | 15-01-1998 | AU 3847997 A | 02-02-1998 |
| | | CA 2259149 A | 15-01-1998 |
| | | EP 0958305 A | 24-11-1999 |

# PATENT COOPERATION TREATY

# PCT



# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

15

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| PHM70385/WO | | |
| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
| PCT/GB99/02957 | 07/09/1999 | 12/09/1998 |
| International Patent Classification (IPC) or national classification and IPC | | |
| C07K5/08 | | |
| Applicant | | |
| Astra Zeneca UK Limited et al | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 11 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 14/03/2000 | 21.11.2000 |
| Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 | Authorized officer |

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/02957

## I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
**Description, pages:**

| | | | | |
|---|---|---|---|---|
| 1-8,12-43 | as originally filed | | | |
| 9-11 | as received on | 18/07/2000 | with letter of | 18/07/2000 |

**Claims, No.:**

| | | | | |
|---|---|---|---|---|
| 1-17 | as received on | 18/07/2000 | with letter of | 18/07/2000 |

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   *(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-17 |
| | No: | Claims | |
| Inventive step (IS) | Yes: | Claims | 1-17 |
| | No: | Claims | |
| Industrial applicability (IA) | Yes: | Claims | 1-12,14,16,17 |
| | No: | Claims | 13,15 (see Separate Sheet, point V) |

2. Citations and explanations
   **see separate sheet**

## VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
**see separate sheet**

Re Item V

**Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

Reference is made to the following document:

D1: WO,A,98 01467

**1. Novelty**

The prior art does not disclose compounds according to general formula (1) as defined in claim 1 and dependent claims.

The present application does therefore satiesfy the criterion as set forth in Art. 33(2) PCT, because the subject-matter of claims 1-17 is new.

**2. Inventive Step**

The present application does furthermore satiesfy the criterion as set forth in Art. 33(3) PCT, because the subject-matter of claims 1-17 is regarded as inventive.

In view of document D1, which discloses peptides comprising at least 10 amino acids, which inhibit the interaction between MDM2 and the tumor suppressor protein p53 and which is regarded as representing the closest prior art, the problem underlying the present application can be defined as providing alternative compounds with the same activity. To solve this problem, the applicant provides the compounds as defined in

For the assessment of the present claims 13 and 15 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**Re Item VII**

**Certain defects in the international application**

Page 4 of the description should have been brought in conformity with the amended set of claims; this means (S)-4-chloro-N-[1-(1H-indol-3-ylmethyl)-2-oxo-2-(4-phenyl-1-piperazinyl)ethyl]-N-methyl-benzamide should have been also excluded on page 4 of the description.

A further preferred group of compounds of the invention include, for example a compound of formula (1) wherein $R_5$ is $R_6CH_2$– and $R_6$ is $R_7$, or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

(a) $R_1$ is hydrogen; $R_2$ is nitro; $R_3$ is hydrogen; $R_4$ is indole; N-($C_{1-4}$alkyl)indole; cyclohexyl or halo-phenyl; $R_5$ is $R_6CH_2$–; $R_6$ is $R_7$; $R_7$ is of formula (3); $R_{10}$ is either a $C_{3-7}$ carbocyclic ring or a $C_{1-4}$alkyl chain; $R_{11}$ is hydrogen; $L_4$ is hydrogen or methyl and r is 1.

A more preferred compound of the invention is a compound of formula (1) wherein $R_5$ is $R_6C(O)$ – and $R_6$ is a substituted phenyl group, or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

$R_1$ is hydrogen; $R_2$ is nitro; $R_3$ is hydrogen; $R_4$ is indole; N-($C_{1-4}$alkyl)indole; or 4-chloro-phenyl; $R_5$ is $R_6C(O)$–; $R_6$ is 4,5-dimethoxy-2-nitrophenyl; $L_1$ is hydrogen or methyl; n is 1 and where the optical centre represented in the Formula (X) is in the S configuration.

A further more preferred compound of the invention is a compound of formula (1) wherein $R_5$ is $R_6C(O)$– and $R_6$ is $R_7$ and $R_7$ is of formula (2), or a pharmaceutically acceptable salts, prodrugs or solvates thereof, wherein:

$R_1$ is hydrogen; $R_2$ is nitro; $R_3$ is hydrogen; $R_4$ is indole; N-($C_{1-4}$alkyl)indole; phenyl; 4-chloro-phenyl or cyclohexyl; $R_5$ is $R_6C(O)$–; $R_6$ is $R_7$; $R_7$ is of formula (2); $R_8$ is amino; $A_1$ is oxygen or a bond; $R_9$ is phenyl or cyclohexyl; $R_{11}$ is hydrogen; $L_1$, $L_2$ and $L_3$ are independently hydrogen or methyl; n is 1; q is 2 - 4 and p is 0-1.

Particular compounds of the invention are:

2-methyl-3-nitrobenzoyl-Trp-piperazine-4-nitrophenyl;

2,4-dimethyl-benzoyl-Trp-piperazine-4-nitrophenyl;

5-bromo-2-furoyl-Trp-piperazine-4-nitrophenyl;

2-methoxybenzoyl-Trp-piperazine-4-nitrophenyl;

dimethoxynitrobenzoyl-Trp-piperazine-4-nitrophenyl;

2-methyl-3-furoyl-Trp-piperazine-4-nitrophenyl;

thiophene-3-carboxyl-Trp-piperazine-4-nitrophenyl;

2-(methylthio)-nicotinoyl-Trp-piperazine-4-nitrophenyl;

3-chlorothiophene-2-carboxyl-Trp-piperazine-4-nitrophenyl;

2,5-dimethoxybenzoyl-Trp-piperazine-4-nitrophenyl;

2-benzofuroyl-Trp-piperazine-4-nitrophenyl;

N-methylpyrrole-2-carboxyl-Trp-piperazine-4-nitrophenyl;

2-bromo-5-methoxybenzoyl-Trp-piperazine-4-nitrophenyl;

thiophene-2-carboxyl-Trp-piperazine-4-nitrophenyl;

5-chlorothiophene-2-carboxyl-Trp-piperazine-4-nitrophenyl;

2-methoxy-4-nitrobenzoyl-Trp-piperazine-4-nitrophenyl;

2-furylcarbonyl-Trp-piperazine-4-nitrophenyl;

6-methylpicoliny-Trp-piperazine-4-nitrophenyl;

3-methoxy-2-nitrobenzoyl-Trp-piperazine-4-nitrophenyl;

Dimethoxynitrobenzoyl-(D)Trp-piperazine-4-nitrophenyl;

4-oxo-4H-1-benzopyran-2-caboxyl-Trp-piperazine-4-nitrophenyl;

5-nitro-2-furoyl-Trp-piperazine-4-nitrophenyl;

1,2,3-thiadiazole-4-carboxyl-Trp-piperazine-4-nitrophenyl;

Z-Lys-(NMe)Phe-Trp-piperazine-4-nitrophenyl;

cyclohexylacetyl-(D)Lys-(D)NMe-Phe-(D)Trp-piperazine-4-nitrophenyl;

adamantaneacetyl-(D)Lys-(D)NMe-Phe-(D)Trp-piperazine-4-nitrophenyl;

cycloheptanoyl-(D)Lys-(D)NMe-Phe-(D)Trp-piperazine-4-nitrophenyl;

2-propylpentanoyl-(D)Lys-(D)NMe-Phe-(D)Trp-piperazine-4-nitrophenyl;

Z-(D)NMe-Lys-(D)NMe-Phe-(D)Trp-piperazine-4-nitrophenyl;

$Me_2CHCH_2$(D,L)NME-Phe{$CH_2NH$}(D)Trp-piperazine-4-nitrophenyl;

Z-LYS-(NMe)Phe-(D)Trp-piperazine-4-nitrophenyl;

cyclohexyl-(D)Lys-(D)(NMe)Phe-(D)Trp-piperazine-4-nitrophenyl;

T-butylacetyl-(D)Lys-(D)NMePhe-(D)Trp-piperazine-4-nitrophenyl;

cyclohexyl-(D)Lys-(D)NMe-Phe-(D)Phe(4-Cl)-piperazine-dichlorophenyl; and

cyclohexyl-(D)Lys-(D)NMePhe-(D)Tyr(Et)-piperazine-4-nitrophenyl;

or a pharmaceutically acceptable salt, prodrug or solvate thereof.

Further particular compounds of the invention are:

4,5-dimethoxy-2-nitrobenzoyl-Phe(4-Cl)-piperazine-4-nitrophenyl;

4,5-dimethoxy-2-nitrobenzoyl-NMe-Trp-piperazine-4-nitrophenyl;

4,5-dimethoxy-2-nitrobenzoyl-(D)($N^{in}$-Me)Trp-piperazine-4-nitrophenyl;

Z-(D)(NMe)Dab-(NMe)(D)Phe-(D)Trp-piperazine-4-nitrophenyl;

Z-NMe(D)Lys-NMe(D)Phe-(D)Phe(4-Cl)-piperazine-4-nitrophenyl;
cyclohexyl-CO-(D)Lys-(D)NMe-Phe-Cha-piperazine-4-nitrophenyl;
cyclohexyl-(D)Lys-(D)(NMe)Phe-(D)Phe(4-Cl)-piperazine-4-nitrophenyl;
cyclohexyl-$CH_2$-(D,L)NMe-Phe{$CH_2NH$}(D)Trp-piperazine-4-nitrophenyl; and
cyclohexyl-(D)Lys-(D)(NMe)Phe-(D)hPhe-piperazine-4-nitrophenyl;
or a pharmaceutically acceptable salt, prodrug or solvate thereof.

A suitable pharmaceutically-acceptable salt of a compound of the Formula (1) is, for example, an acid-addition salt of a compound of the Formula (1) which is sufficiently basic, for example an acid-addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, trifluoroacetic, citric or maleic acid; or, for example a salt of a compound of the Formula (1) which is sufficiently acidic, for example an alkali or alkaline earth metal salt such as a calcium or magnesium salt, or an ammonium salt, or a salt with an organic base such as methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

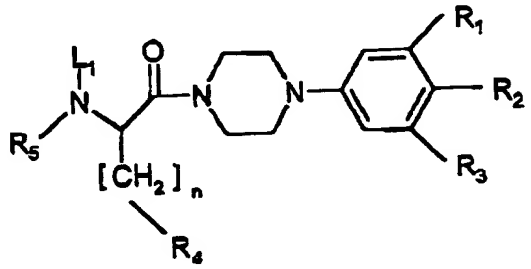
Various forms of prodrugs are known in the art, for example in-vivo hydrolysable esters.

In vivo hydrolysable derivatives include, in particular, pharmaceutically acceptable derivatives that may be oxidised or reduced in the human body to produce the parent compound or esters that hydrolyse in the human body to produce the parent compound. Such esters can be identified by administering, for example, intravenously to the test animal, the compound under test and subsequently examining the test animal's body fluids. Suitable in vivo hydrolysable esters for hydroxy include acetyl and for carboxyl include, for example, alkyl esters, dialkylaminoalkoxy esters, esters of formula -C(O)-O-CH2C(O)NRa"Rb" where Ra" and Rb" are, for example, selected from hydrogen and C1-4 alkyl, and C1-6alkoxy methyl esters for example methoxymethyl, C1-6alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C3-8 cycloalkoxycarbonyloxyC1-6alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolan-2-ylmethyl esters for example 5-methyl-1,3-diox lan-2-ylmethyl; and C1-6alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl.

For examples of prodrug derivatives, see:

## REVISED CLAIMS

1. A compound of formula (1):



formula (1)

wherein :

$L_1$ is hydrogen or methyl;

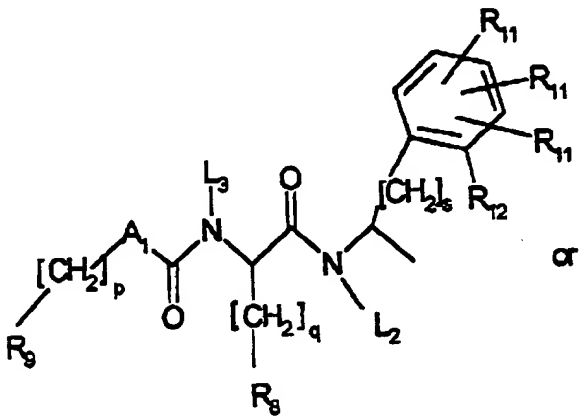
$R_1$ and $R_2$ and $R_3$ are each independently hydrogen, halo, nitro, cyano, carbamoyl, N-($C_{1-4}$alkyl)carbamoyl, NN-(di$C_{1-4}$alkyl)carbamoyl or $C_{1-4}$alkoxycarbonyl;

$R_4$ is indole, N-($C_{1-4}$ alkyl) indole, $C_{5-7}$carbocyclic ring or aryl, any of which can be optionally substituted on ring carbon atoms with up to three substituents each independently selected from halo, $C_{1-4}$alkyl, or $C_{1-4}$alkoxy;

$R_5$ is hydrogen, $C_{1-4}$alkyl, $R_6CH_2$– or $R_6C(O)$–;

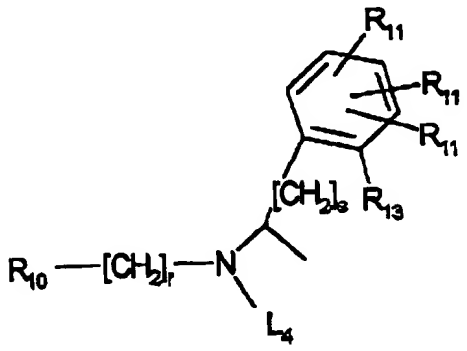
$R_6$ is aryl, heteroaryl, heterocyclyl, amino$C_{3-6}$alkyl, N-($C_{1-4}$alkyl)amino$C_{3-6}$alkyl, NN-(di$C_{1-4}$alkyl)amino$C_{3-6}$alkyl, or $R_7$; wherein the aryl, heteroaryl or heterocyclyl rings may be optionally substituted with up to three substituents independently selected from nitro, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, halo, ($C_{1-4}$alkyl)sulfanyl, $C_{1-4}$ alkoxycarbonyl, N-($C_{1-4}$ alkyl)carbamoyl, NN-(di$C_{1-4}$ alkyl)carbamoyl, N-($C_{1-4}$ alkyl)amino or NN-(di$C_{1-4}$ alkyl)amino;

wherein $R_7$ is either a group of formula (2) of formula (3):



Formula (2)

or



Formula (3)

wherein:

$L_2$, $L_3$ and $L_4$ are each independently hydrogen or methyl;

$R_8$ is amino, guanadino, imidazolo, any of which can be mono or di-N-substituted with $C_{1-4}$alkyl;

$A_1$ is oxygen or a direct bond;

$R_9$ is a $C_{5-8}$ membered mono-carbocyclic ring, a $C_{6-10}$ membered bi-carbocyclic ring, $C_{8-12}$ membered tri-carbocyclic ring, $C_{5-7}$alkyl or aryl, any of which can be optionally mono, bi or tri substituted by $C_{1-4}$ alkyl;

$R_{10}$ is $C_{1-6}$alkyl or a $C_{3-8}$mono-carbocyclic ring;

$R_{11}$ is hydrogen, halo, $C_{1-4}$alkyl, or $C_{1-4}$alkoxy;

$R_{12}$ is hydrogen or methyl or ethyl or $R_{12}$ together with $L_2$ forms a $C_{5-7}$ nitrogen-containing heterocyclic ring;

$R_{13}$ is hydrogen or methyl ethyl or $R_{13}$ together with $L_4$ forms a $C_{5-7}$ nitrogen-containing heterocyclic ring;

n is 0, 1 or 2;

p is 0, 1 or 2;

q is an integer from 1 to 6

r is 0, 1 or 2;

s is 0, 1 or 2;

provided that when $R_6$ is aryl, heteroaryl, heterocyclyl, amino$C_{3-6}$alkyl, N-($C_{1-4}$alkyl)amino$C_{3-6}$alkyl or NN-(di$C_{1-4}$alkyl)amino$C_{3-6}$alkyl then $R_5$ is other than $R_6CH_2$—; and when $R_1$ to $R_3$ are each hydrogen, $L_1$ is hydrogen, n is1, $R_4$ is phenyl, $R_5$ is $R_6C(O)$—, then $R_6$ cannot be 2-methyl-4-amino-butyl,

and excluding (S)-4-chloro-N-[1-(1H-indol-3-ylmethyl)-2-oxo-2-(4-phenyl-1-piperazinyl)ethyl]-N-methyl-benzamide;

or a pharmaceutically acceptable salt, prodrug or solvate thereof.

2. A compound according to claim 1 wherein $R_5$ is hydrogen.

3 A compound according to claim 2 wherein $R_1$ is hydrogen; $R_2$ is nitro; $R_3$ is hydrogen; n is 1; $R_4$ is indole, N-($C_{1-4}$ alkyl)indole, cyclohexyl or phenyl any of which can be optionally substituted on ring carbon atoms with up to three substituents each independently selected from halo, $C_{1-4}$alkyl, or $C_{1-4}$alkoxy, $L_1$ is hydrogen and $R_5$ is hydrogen.

4. A compound according to claim 1 wherein $R_5$ is $R_6C(O)$—; $R_6$ is aryl, heteroaryl, heterocyclyl, amino$C_{3-6}$alkyl, N-($C_{1-4}$alkyl)amino$C_{3-6}$alkyl, or NN-(di$C_{1-4}$alkyl)amino$C_{3-6}$alkyl, wherein the aryl, heteroaryl or heterocyclyl rings can be optionally substituted on ring carbon atoms with up to three substituents each independently selected from nitro, halo, $C_{1-4}$alkyl, or $C_{1-4}$alkoxy.

5. A compound according to claim 4 wherein $R_1$ is hydrogen; $R_2$ is nitro; $R_3$ is hydrogen; n is 1; $L_1$ is hydrogen; and $R_6$ is aryl or heteroaryl wherein the aryl or heteroaryl can be optionally substituted on ring carbon atoms with up to three substituents each independently selected from nitro, halo, $C_{1-4}$alkyl, or $C_{1-4}$alkoxy.

6. A compound according to claim 1 wherein $R_6$ is $R_7$.

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7. A compound according to claim 6 wherein $R_7$ is of Formula (2)

8. A compound according to claim 7 wherein $R_1$ is hydrogen; $R_2$ is nitro; $R_3$ is hydrogen; n is 1; $L_1$ is hydrogen; $L_2$ is hydrogen or methyl; q is an integer between 2 and 4; $R_8$ is amino; s is 1 and $L_3$ is hydrogen or methyl.

9. A compound according to claim 6 wherein $R_7$ is of Formula (3).

10. A compound according to claim 9 wherein $R_1$ is hydrogen; $R_2$ is nitro; $R_3$ is hydrogen; n is 1; s is 1 and $L_1$ is hydrogen,

11. A compound selected from the following:

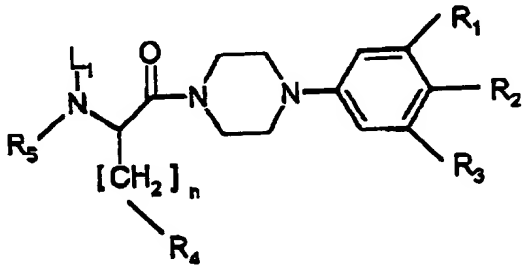
4,5-dimethoxy-2-nitrobenzoyl-Phe(4-Cl)-piperazine-4-nitrophenyl;
4,5-dimethoxy-2-nitrobenzoyl-NMe-Trp-piperazine-4-nitrophenyl;
4,5-dimethoxy-2-nitrobenzoyl-(D)($N^{in}$-Me)Trp-piperazine-4-nitrophenyl;
Z-(D)(NMe)Dab-(NMe)(D)Phe-(D)Trp-piperazine-4-nitrophenyl;
Z-NMe(D)Lys-NMe(D)Phe-(D)Phe(4-Cl)-piperazine-4-nitrophenyl;
cyclohexyl-CO-(D)Lys-(D)NMe-Phe-Cha-piperazine-4-nitrophenyl;
cyclohexyl-(D)Lys-(D)(NMe)Phe-(D)Phe(4-Cl)-piperazine-4-nitrophenyl;
cyclohexyl-$CH_2$-(D,L)NMe-Phe{$CH_2NH$}(D)Trp-piperazine-4-nitrophenyl; and
cyclohexyl-(D)Lys-(D)(NMe)Phe-(D)hPhe-piperazine-4-nitrophenyl;

or a pharmaceutically acceptable salt, prodrug or solvate thereof.

12. A pharmaceutical composition which comprises a compound according to claims 1 to 11 and a pharmaceutically acceptable carrier.

13. The use in the treatment of a warm-blooded animal, by therapy, a compound of formula (1), or a pharmaceutically acceptable salt, prodrug or solvate thereof.

14. The use of a compound of Formula (4) in the manufacture of a medicament for the treatment of cancer in a warm-blooded animal.



formula (4)

wherein :

$L_1$ is hydrogen or methyl;

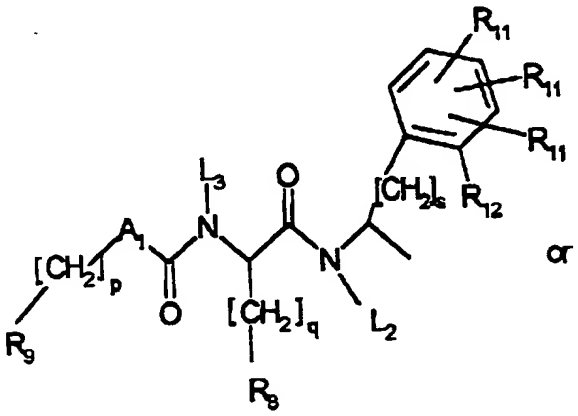
$R_1$ and $R_2$ and $R_3$ are each independently hydrogen, halo, nitro, cyano, carbamoyl, N-($C_{1-4}$alkyl)carbamoyl, NN-(di$C_{1-4}$alkyl)carbamoyl or $C_{1-4}$alkoxycarbonyl;

$R_4$ is indole, N-($C_{1-4}$ alkyl) indole, $C_{5-7}$carbocyclic ring or aryl, any of which can be optionally substituted on ring carbon atoms with up to three substituents each independently selected from halo, $C_{1-4}$alkyl, or $C_{1-4}$alkoxy;

$R_5$ is hydrogen, $C_{1-4}$alkyl, $R_6CH_2$– or $R_6C(O)$–;

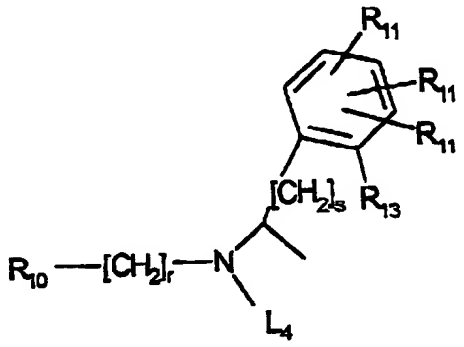
$R_6$ is aryl, heteroaryl, heterocyclyl, amino$C_{3-6}$alkyl, N-($C_{1-4}$alkyl)amino$C_{3-6}$alkyl, NN-(di$C_{1-4}$alkyl)amino$C_{3-6}$alkyl, or $R_7$; wherein the aryl, heteroaryl or heterocyclyl rings may be optionally substituted with up to three substituents independently selected from nitro, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, halo, ($C_{1-4}$alkyl)sulfanyl, $C_{1-4}$ alkoxycarbonyl, N-($C_{1-4}$ alkyl)carbamoyl, NN-(di$C_{1-4}$ alkyl)carbamoyl, N-($C_{1-4}$ alkyl)amino or NN-(di$C_{1-4}$ alkyl)amino;

wherein $R_7$ is either a group of formula (5) of formula (6):



Formula (5)

or



Formula (6)

wherein:

$L_2$, $L_3$ and $L_4$ are each independently hydrogen or methyl;

$R_8$ is amino, guanadino, imidazolo, any of which can be mono or di-N-substituted with $C_{1-4}$alkyl;

$A_1$ is oxygen or a direct bond;

$R_9$ is a $C_{5-8}$ membered mono-carbocyclic ring, a $C_{6-10}$ membered bi-carbocyclic ring, $C_{8-12}$ membered tri-carbocyclic ring, $C_{5-7}$alkyl or aryl, any of which can be optionally mono, bi or tri substituted by $C_{1-4}$ alkyl;

$R_{10}$ is $C_{1-6}$alkyl or a $C_{3-8}$mono-carbocyclic ring;

$R_{11}$ is hydrogen, halo, $C_{1-4}$alkyl, or $C_{1-4}$alkoxy;

$R_{12}$ is hydrogen or methyl or ethyl or $R_{12}$ together with $L_2$ forms a $C_{5-7}$ nitrogen-containing heterocyclic ring;

$R_{13}$ is hydrogen or methyl ethyl or $R_{13}$ together with $L_4$ forms a $C_{5-7}$ nitrogen-containing heterocyclic ring;

n is 0, 1 or 2;

p is 0, 1 or 2;

q is an integer from 1 to 6

r is 0, 1 or 2;

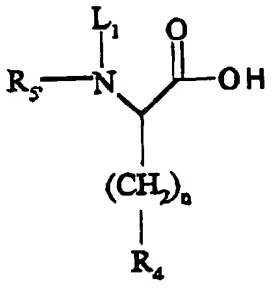
s is 0, 1 or 2;

provided that when $R_6$ is aryl, heteroaryl, heterocyclyl, amino$C_{3-6}$alkyl, N-($C_{1-4}$alkyl)amino$C_{3-6}$alkyl or NN-(di$C_{1-4}$alkyl)amino$C_{3-6}$alkyl then $R_5$ is other than $R_6CH_2$—; or a pharmaceutically acceptable salt, prodrug or solvate thereof.

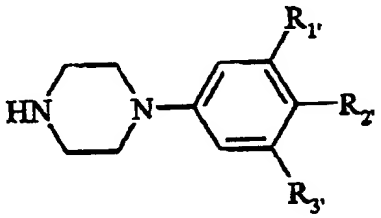
15. A method of treating cancers which comprises administering to a warm-blooded animal an effective amount of a compound of formula (4).

16. A pharmaceutical composition comprising a compound of formula (4), or a pharmaceutically acceptable salt, prodrug or solvate thereof, in admixture with a pharmaceutically-acceptable diluent or carrier for the treatment of cancer in a warm-blooded animal.

17. A process for preparing a compound of the formula (1) or a pharmaceutically acceptable salt, prodrug or solvate thereof which process comprises:
a) reacting a carboxylic acid of Formula (8) or a reactive derivative thereof with a piperazine of formula (9)

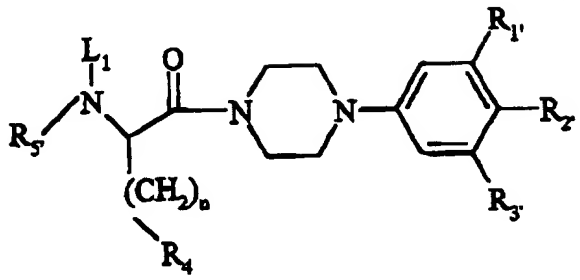


Formula (8)



Formula (9)

wherein $L_1$, n, $R_4$, $R_1$–$R_3$, and $R_5$, are as herein above defined.
To form a compound of Formula (7)



Formula (7)

b) removing any protecting groups,

c) optionally forming a pharmaceutically acceptable salt, prodrug or solvate.

A further preferred group of compounds of the invention include, for example a compound of formula (1) wherein $R_5$ is $R_6CH_2$– and $R_6$ is $R_7$, or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

(a) $R_1$ is hydrogen; $R_2$ is nitro; $R_3$ is hydrogen; $R_4$ is indole; N-($C_{1-4}$alkyl)indole; cyclohexyl or halo-phenyl; $R_5$ is $R_6CH_2$–; $R_6$ is $R_7$; $R_7$ is of formula (3); $R_{10}$ is either a $C_{3-7}$ carbocyclic ring or a $C_{1-4}$alkyl chain; $R_{11}$ is hydrogen; $L_4$ is hydrogen or methyl and r is 1.

A more preferred compound of the invention is a compound of formula (1) wherein $R_5$ is $R_6C(O)$ – and $R_6$ is a substituted phenyl group, or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

$R_1$ is hydrogen; $R_2$ is nitro; $R_3$ is hydrogen; $R_4$ is indole; N-($C_{1-4}$alkyl)indole; or 4-chloro-phenyl; $R_5$ is $R_6C(O)$–; $R_6$ is 4,5-dimethoxy-2-nitrophenyl; $L_1$ is hydrogen or methyl; n is 1 and where the optical centre represented in the Formula (X) is in the S configuration.

A further more preferred compound of the invention is a compound of formula (1) wherein $R_5$ is $R_6C(O)$– and $R_6$ is $R_7$ and $R_7$ is of formula (2), or a pharmaceutically acceptable salts, prodrugs or solvates thereof, wherein:

$R_1$ is hydrogen; $R_2$ is nitro; $R_3$ is hydrogen; $R_4$ is indole; N-($C_{1-4}$alkyl)indole; phenyl; 4-chloro-phenyl or cyclohexyl; $R_5$ is $R_6C(O)$–; $R_6$ is $R_7$; $R_7$ is of formula (2); $R_8$ is amino; $A_1$ is oxygen or a bond; $R_9$ is phenyl or cyclohexyl; $R_{11}$ is hydrogen; $L_1$, $L_2$ and $L_3$ are independently hydrogen or methyl; n is 1; q is 2 - 4 and p is 0-1.

Particular compounds of the invention are:

2-methyl-3-nitrobenzoyl-TRP-piperazine-4-nitrophenyl;

2,4-dimethyl-benzoyl-TRP-piperazine-4-nitrophenyl;

5-bromo-2-furoyl-TRP-piperazine-4-nitrophenyl;

2-methoxybenzoyl-TRP-piperazine-4-nitrophenyl;

dimethoxynitrobenzoyl-TRP-piperazine-4-nitrophenyl;

2-methyl-3-furoyl-TRP-piperazine-4-nitrophenyl;

thiophene-3-carboxyl-TRP-piperazine-4-nitrophenyl;

2-(methylthio)-nicotinoyl-TRP-piperazine-4-nitrophenyl;

3-chlorothiophene-2-carboxyl-TRP-piperazine-4-nitrophenyl;

2,5-dimethoxybenzoyl-TRP-piperazine-4-nitrophenyl;

2-benzofuroyl-TRP-piperazine-4-nitrophenyl;

N-methylpyrrole-2-carboxyl-TRP-piperazine-4-nitrophenyl;

2-bromo-5-methoxybenzoyl-TRP-piperazine-4-nitrophenyl;

thiophene-2-carboxyl-TRP-piperazine-4-nitrophenyl;

5-chlorothiophene-2-carboxyl-TRP-piperazine-4-nitrophenyl;

2-methoxy-4-nitrobenzoyl-TRP-piperazine-4-nitrophenyl;

2-furylcarbonyl-TRP-piperazine-4-nitrophenyl;

6-methylpicoliny-TRP-piperazine-4-nitrophenyl;

3-methoxy-2-nitrobenzoyl-TRP-piperazine-4-nitrophenyl;

Dimethoxynitrobenzoyl-(D)TRP-piperazine-4-nitrophenyl;

4-oxo-4H-1-benzopyran-2-caboxyl-TRP-piperazine-4-nitrophenyl;

5-nitro-2-furoyl-TRP-piperazine-4-nitrophenyl;

1,2,3-thiadiazole-4-carboxyl-TRP-piperazine-4-nitrophenyl;

Z-LYS-(NMe)PHE-TRP-piperazine-4-nitrophenyl;

cyclohexylacetyl-(D)LYS-(D)NMe-PHE-(D)TRP-piperazine-4-nitrophenyl;

adamantaneacetyl-(D)LYS-(D)NMe-PHE-(D)TRP-piperazine-4-nitrophenyl;

cycloheptanoyl-(D)LYS-(D)NMe-PHE-(D)TRP-piperazine-4-nitrophenyl;

2-propylpentanoyl-(D)LYS-(D)NMe-PHE-(D)TRP-piperazine-4-nitrophenyl;

Z-(D)NMe-LYS-(D)NMe-PHE-(D)TRP-piperazine-4-nitrophenyl;

$Me_2CHCH_2$(D,L)NME-PHE{$CH_2NH$}(D)TRP-piperazine-4-nitrophenyl;

Z-LYS-(NMe)PHE-(D)TRP-piperazine-4-nitrophenyl;

cyclohexyl-(D)LYS-(D)(NMe)PHE-(D)TRP-piperazine-4-nitrophenyl;

T-butylacetyl-(D)LYS-(D)NMePHE-(D)TRP-piperazine-4-nitrophenyl;

cyclohexyl-(D)LYS-(D)NMe-PHE-(D)PHE(4-Cl)-piperazine-dichlorophenyl; and

cyclohexyl-(D)Lys-(D)NMePhe-(D)Tyr(Et)-piperazine-4-nitrophenyl;

or a pharmaceutically acceptable salt, prodrug or solvate thereof.

Further particular compounds of the invention are:

4,5-dimethoxy-2-nitrobenzoyl-PHE(4-Cl)-piperazine-4-nitrophenyl;

4,5-dimethoxy-2-nitrobenzoyl-NMe-TRP-piperazine-4-nitrophenyl;

4,5-dimethoxy-2-nitrobenzoyl-(D)($N^{in}$-Me)TRP-piperazine-4-nitrophenyl;

Z-(D)(NMe)DAB-(NMe)(D)PHE-(D)TRP-piperazine-4-nitrophenyl;

Z-NMe(D)LYS-NMe(D)PHE-(D)PHE(4-Cl)-piperazine-4-nitrophenyl;

cyclohexyl-CO-(D)LYS-(D)NMe-PHE-CHA-piperazine-4-nitrophenyl;

cyclohexyl-(D)Lys-(D)(NMe)Phe-(D)Phe(4-Cl)-piperazine-4-nitrophenyl;

cyclohexyl-$CH_2$-(D,L)NMe-PHE{$CH_2NH$}(D)TRP-piperazine-4-nitrophenyl; and

cyclohexyl-(D)Lys-(D)(NMe)Phe-(D)hPhe-piperazine-4-nitrophenyl;

or a pharmaceutically acceptable salt, prodrug or solvate thereof.

A suitable pharmaceutically-acceptable salt of a compound of the Formula (1) is, for example, an acid-addition salt of a compound of the Formula (1) which is sufficiently basic, for example an acid-addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, trifluoroacetic, citric or maleic acid; or, for example a salt of a compound of the Formula (1) which is sufficiently acidic, for example an alkali or alkaline earth metal salt such as a calcium or magnesium salt, or an ammonium salt, or a salt with an organic base such as methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

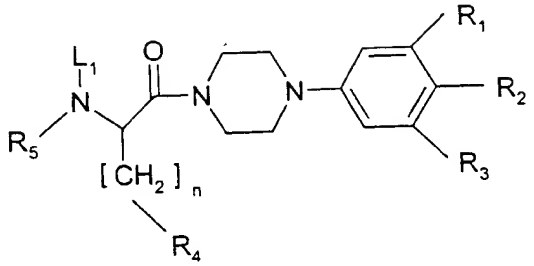
Various forms of prodrugs are known in the art, for example in-vivo hydrolysable esters.

In vivo hydrolysable derivatives include, in particular, pharmaceutically acceptable derivatives that may be oxidised or reduced in the human body to produce the parent compound or esters that hydrolyse in the human body to produce the parent compound. Such esters can be identified by administering, for example, intravenously to the test animal, the compound under test and subsequently examining the test animal's body fluids. Suitable in vivo hydrolysable esters for hydroxy include acetyl and for carboxyl include, for example, alkyl esters, dialkylaminoalkoxy esters, esters of formula -C(O)-O-CH2C(O)NRa"Rb" where Ra" and Rb" are, for example, selected from hydrogen and C1-4 alkyl, and C1-6alkoxy methyl esters for example methoxymethyl, C1-6alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C3-8 cycloalkoxycarbonyloxyC1-6alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolan-2-ylmethyl esters for example 5-methyl-1,3-dioxolan-2-ylmethyl; and C1-6alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl.

For examples of prodrug derivatives, see:

## CLAIMS

1. A compound of formula (1):



formula (1)

wherein :

$L_1$ is hydrogen or methyl;

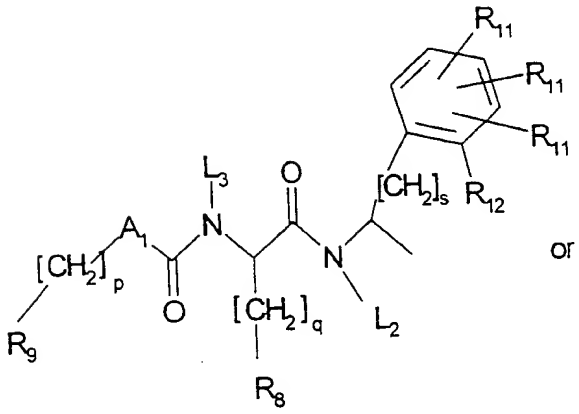
$R_1$ and $R_2$ and $R_3$ are each independently hydrogen, halo, nitro, cyano, carbamoyl, N-($C_{1-4}$alkyl)carbamoyl, NN-(di$C_{1-4}$alkyl)carbamoyl or $C_{1-4}$alkoxycarbonyl;

$R_4$ is indole, N-($C_{1-4}$ alkyl) indole, $C_{5-7}$carbocyclic ring or aryl, any of which can be optionally substituted on ring carbon atoms with up to three substituents each independently selected from halo, $C_{1-4}$alkyl, or $C_{1-4}$alkoxy;

$R_5$ is hydrogen, $C_{1-4}$alkyl, $R_6CH_2-$ or $R_6C(O)-$;

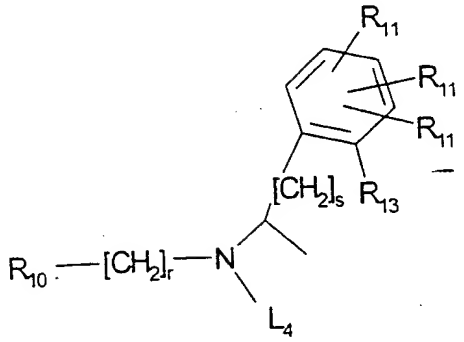
$R_6$ is aryl, heteroaryl, heterocyclyl, amino$C_{3-6}$alkyl, N-($C_{1-4}$alkyl)amino$C_{3-6}$alkyl, NN-(di$C_{1-4}$alkyl)amino$C_{3-6}$alkyl, or $R_7$; wherein the aryl, heteroaryl or heterocyclyl rings may be optionally substituted with up to three substituents independently selected from nitro, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, halo, ($C_{1-4}$alkyl)sulfanyl, $C_{1-4}$ alkoxycarbonyl, N-($C_{1-4}$ alkyl)carbamoyl, NN-(di$C_{1-4}$ alkyl)carbamoyl, N-($C_{1-4}$ alkyl)amino or NN-(di$C_{1-4}$ alkyl)amino;

wherein $R_7$ is either a group of formula (2) of formula (3):



Formula (2)

or



Formula (3)

wherein:

$L_2$, $L_3$ and $L_4$ are each independently hydrogen or methyl;

$R_8$ is amino, guanadino, imidazolo, any of which can be mono or di-N-substituted with $C_{1-4}$alkyl;

$A_1$ is oxygen or a direct bond;

$R_9$ is a $C_{5-8}$ membered mono-carbocyclic ring, a $C_{6-10}$ membered bi-carbocyclic ring, $C_{8-12}$ membered tri-carbocyclic ring, $C_{5-7}$alkyl or aryl, any of which can be optionally mono, bi or tri substituted by $C_{1-4}$ alkyl;

$R_{10}$ is $C_{1-6}$alkyl or a $C_{3-8}$mono-carbocyclic ring;

$R_{11}$ is hydrogen, halo, $C_{1-4}$alkyl, or $C_{1-4}$alkoxy;

$R_{12}$ is hydrogen or methyl or ethyl or $R_{12}$ together with $L_2$ forms a $C_{5-7}$ nitrogen-containing heterocyclic ring;

$R_{13}$ is hydrogen or methyl ethyl or $R_{13}$ together with $L_4$ forms a $C_{5-7}$ nitrogen-containing heterocyclic ring;

n is 0, 1 or 2;

p is 0, 1 or 2;

q is an integer from 1 to 6

r is 0, 1 or 2;

s is 0, 1 or 2;

provided that when $R_6$ is aryl, heteroaryl, heterocyclyl, amino$C_{3-6}$alkyl, N-($C_{1-4}$alkyl)amino$C_{3-6}$alkyl or NN-(di$C_{1-4}$alkyl)amino$C_{3-6}$alkyl then $R_5$ is other than $R_6CH_2$—; and when $R_1$ to $R_3$ are each hydrogen, $L_1$ is hydrogen, n is1, $R_4$ is phenyl, $R_5$ is $R_6C(O)$—, then $R_6$ cannot be 2-methyl-4-amino-butyl,

or a pharmaceutically acceptable salt, prodrug or solvate thereof.

2. A compound according to claim 1 wherein $R_5$ is hydrogen.

3 A compound according to claim 2 wherein $R_1$ is hydrogen; $R_2$ is nitro; $R_3$ is hydrogen; n is 1; $R_4$ is indole, N-($C_{1-4}$ alkyl)indole, cyclohexyl or phenyl any of which can be optionally substituted on ring carbon atoms with up to three substituents each independently selected from halo, $C_{1-4}$alkyl, or $C_{1-4}$alkoxy, $L_1$ is hydrogen and $R_5$ is hydrogen.

4. A compound according to claim 1 wherein $R_5$ is $R_6C(O)$—; $R_6$ is aryl, heteroaryl, heterocyclyl, amino$C_{3-6}$alkyl, N-($C_{1-4}$alkyl)amino$C_{3-6}$alkyl, or NN-(di$C_{1-4}$alkyl)amino$C_{3-6}$alkyl, wherein the aryl, heteroaryl or heterocyclyl rings can be optionally substituted on ring carbon atoms with up to three substituents each independently selected from nitro, halo, $C_{1-4}$alkyl, or $C_{1-4}$alkoxy.

5. A compound according to claim 4 wherein $R_1$ is hydrogen; $R_2$ is nitro; $R_3$ is hydrogen; n is 1; $L_1$ is hydrogen; and $R_6$ is aryl or heteroaryl wherein the aryl or heteroaryl can be optionally substituted on ring carbon atoms with up to three substituents each independently selected from nitro, halo, $C_{1-4}$alkyl, or $C_{1-4}$alkoxy.

6. A compound according to claim 1 wherein $R_6$ is $R_7$.

7. A compound according to claim 6 wherein $R_7$ is of Formula (2)

8. A compound according to claim 7 wherein $R_1$ is hydrogen; $R_2$ is nitro; $R_3$ is hydrogen; n is 1; $L_1$ is hydrogen; $L_2$ is hydrogen or methyl; q is an integer between 2 and 4; $R_8$ is amino; s is 1 and $L_3$ is hydrogen or methyl.

9. A compound according to claim 6 wherein $R_7$ is of Formula (3).

10. A compound according to claim 9 wherein $R_1$ is hydrogen; $R_2$ is nitro; $R_3$ is hydrogen; n is 1; s is 1 and $L_1$ is hydrogen,

11. A compound selected from the following:

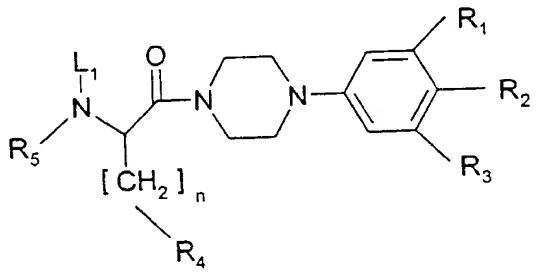
4,5-dimethoxy-2-nitrobenzoyl-PHE(4-Cl)-piperazine-4-nitrophenyl;
4,5-dimethoxy-2-nitrobenzoyl-NMe-TRP-piperazine-4-nitrophenyl;
4,5-dimethoxy-2-nitrobenzoyl-(D)($N^{in}$-Me)TRP-piperazine-4-nitrophenyl;
Z-(D)(NMe)DAB-(NMe)(D)PHE-(D)TRP-piperazine-4-nitrophenyl;
Z-NMe(D)LYS-NMe(D)PHE-(D)PHE(4-Cl)-piperazine-4-nitrophenyl;
cyclohexyl-CO-(D)LYS-(D)NMe-PHE-CHA-piperazine-4-nitrophenyl;
cyclohexyl-(D)Lys-(D)(NMe)Phe-(D)Phe(4-Cl)-piperazine-4-nitrophenyl;
cyclohexyl-$CH_2$-(D,L)NMe-PHE{$CH_2NH$}(D)TRP-piperazine-4-nitrophenyl; and
cyclohexyl-(D)Lys-(D)(NMe)Phe-(D)hPhe-piperazine-4-nitrophenyl;

or a pharmaceutically acceptable salt, prodrug or solvate thereof.

12. A pharmaceutical composition which comprises a compound according to claims 1 to 11 and a pharmaceutically acceptable carrier.

13. The use in the treatment of a warm-blooded animal, by therapy, a compound of formula (1), or a pharmaceutically acceptable salt, prodrug or solvate thereof.

14. The use of a compound of Formula (4) in the manufacture of a medicament for the treatment of cancer in a warm-blooded animal.



formula (4)

wherein :

$L_1$ is hydrogen or methyl;

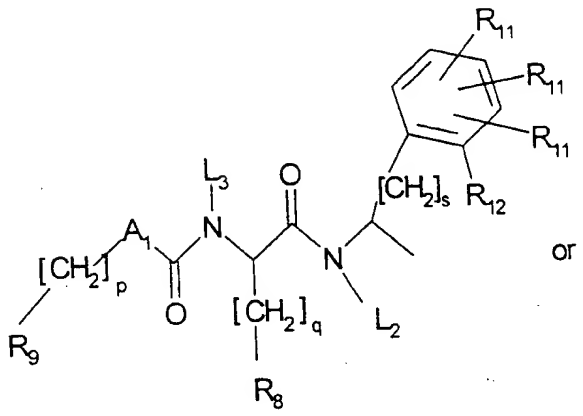
$R_1$ and $R_2$ and $R_3$ are each independently hydrogen, halo, nitro, cyano, carbamoyl, N-($C_{1-4}$alkyl)carbamoyl, NN-(di$C_{1-4}$alkyl)carbamoyl or $C_{1-4}$alkoxycarbonyl;

$R_4$ is indole, N-($C_{1-4}$ alkyl) indole, $C_{5-7}$carbocyclic ring or aryl, any of which can be optionally substituted on ring carbon atoms with up to three substituents each independently selected from halo, $C_{1-4}$alkyl, or $C_{1-4}$alkoxy;

$R_5$ is hydrogen, $C_{1-4}$alkyl, $R_6CH_2$– or $R_6C(O)$–;

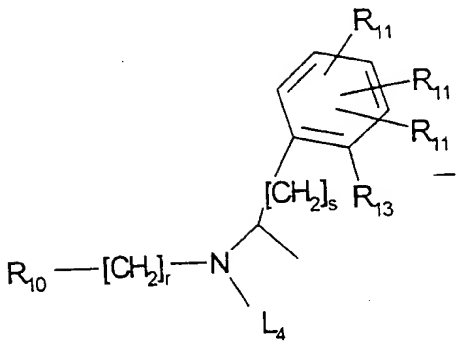
$R_6$ is aryl, heteroaryl, heterocyclyl, amino$C_{3-6}$alkyl, N-($C_{1-4}$alkyl)amino$C_{3-6}$alkyl, NN-(di$C_{1-4}$alkyl)amino$C_{3-6}$alkyl, or $R_7$; wherein the aryl, heteroaryl or heterocyclyl rings may be optionally substituted with up to three substituents independently selected from nitro, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, halo, ($C_{1-4}$alkyl)sulfanyl, $C_{1-4}$ alkoxycarbonyl, N-($C_{1-4}$ alkyl)carbamoyl, NN-(di$C_{1-4}$ alkyl)carbamoyl, N-($C_{1-4}$ alkyl)amino or NN-(di$C_{1-4}$ alkyl)amino;

wherein $R_7$ is either a group of formula (5) of formula (6):



Formula (5)

or



Formula (6)

wherein:

$L_2$, $L_3$ and $L_4$ are each independently hydrogen or methyl;

$R_8$ is amino, guanadino, imidazolo, any of which can be mono or di-N-substituted with $C_{1-4}$alkyl;

$A_1$ is oxygen or a direct bond;

$R_9$ is a $C_{5-8}$ membered mono-carbocyclic ring, a $C_{6-10}$ membered bi-carbocyclic ring, $C_{8-12}$ membered tri-carbocyclic ring, $C_{5-7}$alkyl or aryl, any of which can be optionally mono, bi or tri substituted by $C_{1-4}$ alkyl;

$R_{10}$ is $C_{1-6}$alkyl or a $C_{3-8}$mono-carbocyclic ring;

$R_{11}$ is hydrogen, halo, $C_{1-4}$alkyl, or $C_{1-4}$alkoxy;

$R_{12}$ is hydrogen or methyl or ethyl or $R_{12}$ together with $L_2$ forms a $C_{5-7}$ nitrogen-containing heterocyclic ring;

$R_{13}$ is hydrogen or methyl ethyl or $R_{13}$ together with $L_4$ forms a $C_{5-7}$ nitrogen-containing heterocyclic ring;

n is 0, 1 or 2;

p is 0, 1 or 2;

q is an integer from 1 to 6

r is 0, 1 or 2;

s is 0, 1 or 2;

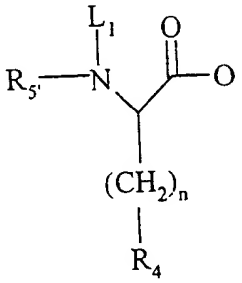
provided that when $R_6$ is aryl, heteroaryl, heterocyclyl, amino$C_{3-6}$alkyl, N-($C_{1-4}$alkyl)amino$C_{3-6}$alkyl or NN-(di$C_{1-4}$alkyl)amino$C_{3-6}$alkyl then $R_5$ is other than $R_6CH_2$—; or a pharmaceutically acceptable salt, prodrug or solvate thereof.

15. A method of treating cancers which comprises administering to a warm-blooded animal an effective amount of a compound of formula (4).

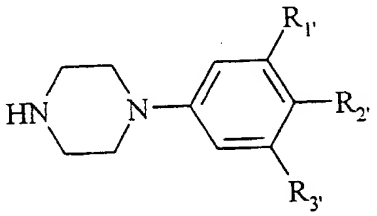
16. A pharmaceutical composition comprising a compound of formula (4), or a pharmaceutically acceptable salt, prodrug or solvate thereof , in admixture with a pharmaceutically-acceptable diluent or carrier for the treatment of cancer in a warm-blooded animal.

17. A process for preparing a compound of the formula (1) or a pharmaceutically acceptable salt, prodrug or solvate thereof which process comprises:

a) reacting a carboxylic acid of Formula (8) or a reactive derivative thereof with a piperazine of formula (9)



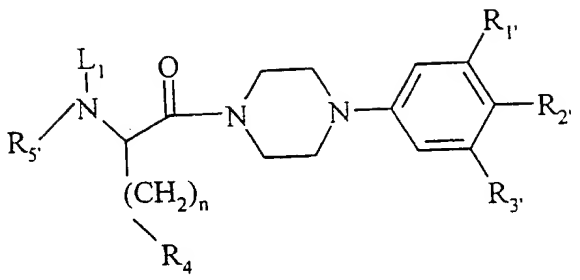
Formula (8)



Formula (9)

wherein $L_1$, n, $R_4$, $R_{1'}$-$R_{3'}$ and $R_{5'}$ are as herein above defined.

To form a compound of Formula (7)



Formula (7)

b) removing any protecting groups,

c) optionally forming a pharmaceutically acceptable salt, prodrug or solvate.

# PCT

## REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* PHM70385/WO

**Box No. I TITLE OF INVENTION**

CHEMICAL COMPOUNDS

**Box No. II APPLICANT**

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

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GB

☐ This person is also inventor.

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State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

**Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)**

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

LUKE, Richard William Arthur
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Cheshire SK10 4TG
GB

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is,country)* of nationality: GB

State *(that is, country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

**Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE**

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

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☐ **Adress for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.



*See Notes to the request form*

**Continuation of B x No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS**

***If none of the following sub-boxes is used, this sheet should not be included in the request.***

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

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GB

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: GB

State *(that is, country)* of residence: GB

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

COTTON, Ronald
Alderley Park
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Cheshire SK10 4TG
GB

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: GB

State *(that is, country)* of residence: GB

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
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Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
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- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☐ the United States of America only
- ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

**Box No. V DESIGNATION OF STATES**

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

**Regional Patent**

- [X] AP **ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- [X] EA **Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- [X] EP **European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- [X] OA **OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

**National Patent** *(if other kind of protection or treatment desired, specify on dotted line)*:

- [X] AL Albania
- [X] AM Armenia
- [X] AT Austria
- [X] AU Australia
- [X] AZ Azerbaijan
- [X] BA Bosnia and Herzegovina
- [X] BB Barbados
- [X] BG Bulgaria
- [X] BR Brazil
- [X] BY Belarus
- [X] CA Canada
- [X] CH and LI Switzerland and Liechtenstein
- [X] CN China
- [X] CU Cuba
- [X] CZ Czech Republic
- [X] DE Germany
- [X] DK Denmark
- [X] EE Estonia
- [X] ES Spain
- [X] FI Finland
- [X] GB United Kingdom
- [X] GD Grenada
- [X] GE Georgia
- [X] GH Ghana
- [X] GM Gambia
- [X] HR Croatia
- [X] HU Hungary
- [X] ID Indonesia
- [X] IL Israel
- [X] IN India
- [X] IS Iceland
- [X] JP Japan
- [X] KE Kenya
- [X] KG Kyrgyzstan
- [X] KP Democratic People's Republic of Korea
- [X] KR Republic of Korea
- [X] KZ Kazakhstan
- [X] LC Saint Lucia
- [X] LK Sri Lanka
- [X] LR Liberia
- [X] LS Lesotho
- [X] LT Lithuania
- [X] LU Luxembourg
- [X] LV Latvia
- [X] MD Republic of Moldova
- [X] MG Madagascar
- [X] MK The former Yugoslav Republic of Macedonia
- [X] MN Mongolia
- [X] MW Malawi
- [X] MX Mexico
- [X] NO Norway
- [X] NZ New Zealand
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- [X] RU Russian Federation
- [X] SD Sudan
- [X] SE Sweden
- [X] SG Singapore
- [X] SI Slovenia
- [X] SK Slovakia
- [X] SL Sierra Leone
- [X] TJ Tajikistan
- [X] TM Turkmenistan
- [X] TR Turkey
- [X] TT Trinidad and Tobago
- [X] UA Ukraine
- [X] UG Uganda
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- [X] ZA South Africa
- [X] DM Dominica
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*See Notes to the request form*

**Box No. VI PRIORITY CLAIM** ☐ Further priority claims are indicated in the Supplemental Box.

| Filing date of earlier application (day/month/year) | Number of earlier application | Where earlier application is: national application: country | regional application:* regional Office | international application: receiving Office |
|---|---|---|---|---|
| item (1) 12SEP98 | 9819860.9 | GB | | |
| item (2) | | | | |
| item (3) | | | | |

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): X Item 1

* *Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

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**Choice of International Searching Authority (ISA)** *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):* ISA /

**Request to use results of earlier search; reference to that search** *(if an earlier search has been carried out by or requested from the International Searching Authority):*
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**Box No. VIII CHECK LIST; LANGUAGE OF FILING**

This international application contains the following **number of sheets**:

| | | |
|---|---|---|
| request | : | 4 |
| description (excluding sequence listing part) | : | 43 |
| claims | : | 8 |
| abstract | : | 3 |
| drawings | : | - |
| sequence listing part of description | : | - |
| **Total number of sheets** | : | 58 |

This international application is **accompanied by** the item(s) marked below:

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2. ☒ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
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8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
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**Figure of the drawings** which should accompany the abstract:

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**Box No. IX SIGNATURE OF APPLICANT OR AGENT**

*Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).*

T. Bryant.

BRYANT, Tracey
Agent for Applicants

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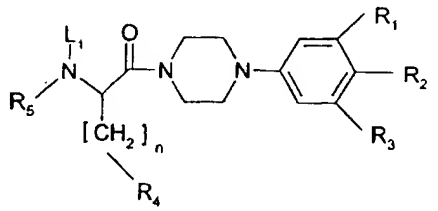
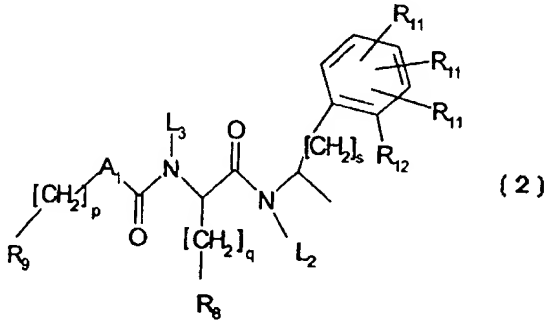


( 1 )



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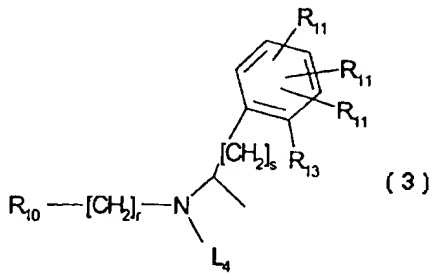

( 3 )

(57) Abstract

A compound of formula (1), wherein: $R_5$ is hydrogen, $C_{1-4}$alkyl, $R_6CH_2$– or $R_6C(O)$–; $R_6$ is aryl, heteroaryl, heterocyclyl, amino$C_{3-6}$alkyl, N–($C_{1-4}$alkyl)amino$C_{3-6}$alkyl, NN–(di$C_{1-4}$alkyl)amino$C_{3-6}$alkyl, or $R_7$; wherein the aryl, heteroaryl or heterocyclyl rings may be optionally substituted with up to three substituents independently selected from nitro, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, halo, ($C_{1-4}$alkyl)sulfanyl, $C_{1-4}$alkoxycarbonyl, N–($C_{1-4}$alkyl)carbamoyl, NN–(di$C_{1-4}$alkyl)carbamoyl, N–($C_{1-4}$alkyl)amino or NN–(di$C_{1-4}$alkyl)amino; wherein $R_7$ is either a group or formula (2) or formula (3); and wherein $L_1$, $L_2$, $L_3$, $L_4$, $R_1$, $R_2$, $R_3$, $R_4$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $A_1$, n, p, q, r and s are as defined in claim 1. The compounds of formula (1) inhibit the interactions between MDM2 and p53 and may be useful in the treatment of cancers.

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# PIPERIZINE-4-PHENYL DERIVATIVES AS INHIBITORS OF THE INTERACTION BETWEEN MDM2 AND 53

This invention relates to compounds which inhibit the interaction between MDM2 and the tumour suppressor protein, p53. This invention also relates to processes for the manufacture of MDM2/p53 interaction inhibitors and pharmaceutically acceptable salts, prodrugs or solvates thereof, to novel pharmaceutical compositions containing them and to the use of the compounds as probes of MDM2 and p53 function.

p53 is a transcription factor which plays a pivotal role in the regulation of the balance between cell proliferation and cell growth arrest/apoptosis. Under normal conditions the half life of p53 is very short and consequently the level of p53 in cells is low. However, in response to cellular DNA damage or cellular stress, levels of p53 increase. This increase in p53 levels leads to the activation of the transcription of a number of genes which induces the cell to either growth arrest or to undergo the processes of apoptosis. Thus the function of p53 is to prevent the proliferation of transformed cells and thus protect the organism from the development of cancer (for a review see Levine 1997, Cell 88, 323-331).

MDM2 is a key negative regulator of p53 function, which binds to the amino terminal transactivation domain of p53. MDM2 both inhibits the ability of p53 to activate transcription and targets p53 for proteolytic degradation, thus maintaining the low levels of p53 under normal conditions. MDM2 may also have separate functions in addition to inhibition of p53. For example, MDM2 also binds another tumour suppressor protein, the retinoblastoma gene product, and inhibits it ability to activate transcription. For reviews of MDM2 function see: Piette et al (1997) Oncogene 15, 1001-1010; Lane and Hall (1997) TIBS 22, 372-374; Lozano and de Oca Luna (1998) Biochim Biophys Acta 1377, M55-M59.

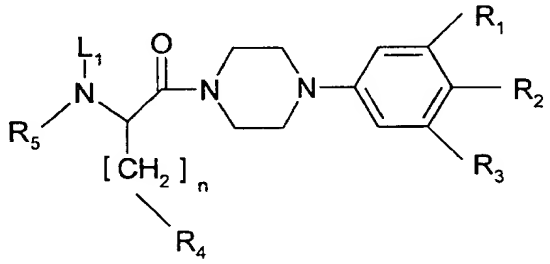
MDM2 is a cellular proto-oncogene. Overexpression of MDM2 has been observed in a range of cancers see Momand and Zambetti (1997) J. Cell. Biochem 64, 343-352. The mechanism by which MDM2 amplification promotes tumourigenesis is at least in part related to its interaction with p53. In cells over-expressing MDM2 the protective function of p53 is blocked and thus cells are unable to respond to DNA damage or cellular stress by increasing p53 levels, leading to cell growth arrest and/or apoptosis. Thus after DNA damage and/or cellular stress cells over-expressing MDM2 are free to continue to proliferate and assume a

tumourigenic phenotype. Under these conditions disruption of the interaction of p53 and MDM2 would release the p53 and thus allow the normal signals of growth arrest and/or apoptosis to function. Thus disruption of the interaction of MDM2 and p53 offers an approach for therapeutic intervention in cancer.

A few patent applications have been published which describe peptide inhibitors of the interaction of p53 and MDM2, see: International Patent Application, WO9602642, University of Dundee; International Patent Application WO 9801467, Novartis & Cancer Research Campaign Technology Ltd.; and International Patent Application WO 9709343.

We have discovered a novel class of small molecule compounds which inhibit the interaction of MDM2 and p53. These compounds are useful as probes of MDM2 and p53 function and may be useful as agents for the treatment of cancer.

According to the invention there is provided a compound of formula (1):




formula (1)

wherein :

$L_1$ is hydrogen or methyl;

$R_1$ and $R_2$ and $R_3$ are each independently hydrogen, halo, nitro, cyano, carbamoyl, N-($C_{1-4}$alkyl)carbamoyl, NN-(di$C_{1-4}$alkyl)carbamoyl or $C_{1-4}$alkoxycarbonyl;

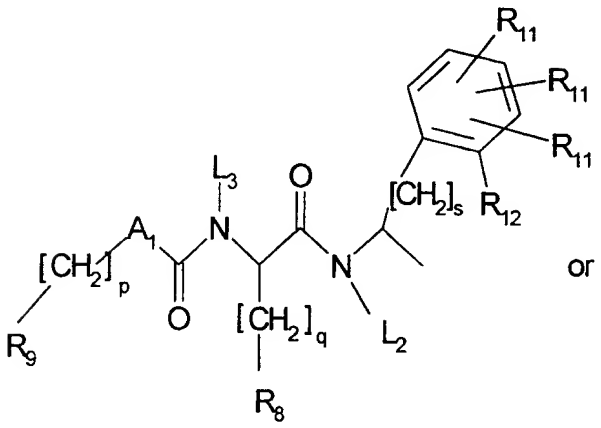
$R_4$ is indole, N-($C_{1-4}$ alkyl) indole, $C_{5-7}$carbocyclic ring or aryl, any of which can be optionally substituted on ring carbon atoms with up to three substituents each independently selected from halo, $C_{1-4}$alkyl, or $C_{1-4}$alkoxy;

$R_5$ is hydrogen, $C_{1-4}$alkyl, $R_6CH_2-$ or $R_6C(O)-$;

$R_6$ is aryl, heteroaryl, heterocyclyl, amino$C_{3-6}$alkyl, N-($C_{1-4}$alkyl)amino$C_{3-6}$alkyl, NN-(di$C_{1-4}$alkyl)amino$C_{3-6}$alkyl, or $R_7$; wherein the aryl, heteroaryl or heterocyclyl rings may be optionally substituted with up to three substituents independently selected from nitro, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, halo, ($C_{1-4}$alkyl)sulfanyl, $C_{1-4}$ alkoxycarbonyl,

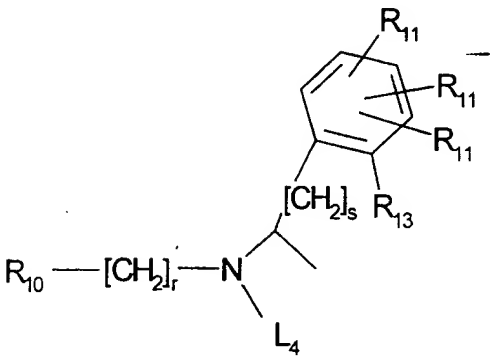
N-($C_{1-4}$ alkyl)carbamoyl, NN-(di$C_{1-4}$ alkyl)carbamoyl, N-($C_{1-4}$ alkyl)amino or NN-(di$C_{1-4}$ alkyl)amino;

wherein $R_7$ is either a group of formula (2) of formula (3):



Formula (2)

or



Formula (3)

wherein:

$L_2$, $L_3$ and $L_4$ are each independently hydrogen or methyl;

$R_8$ is amino, guanadino, imidazolo, any of which can be mono or di-N-substituted with $C_{1-4}$alkyl;

$A_1$ is oxygen or a direct bond;

$R_9$ is a $C_{5-8}$ membered mono-carbocyclic ring, a $C_{6-10}$ membered bi-carbocyclic ring, $C_{8-12}$ membered tri-carbocyclic ring, $C_{5-7}$alkyl or aryl, any of which can be optionally mono, bi or tri substituted by $C_{1-4}$ alkyl;

$R_{10}$ is $C_{1-6}$alkyl or a $C_{3-8}$mono-carbocyclic ring;

$R_{11}$ is hydrogen, halo, $C_{1-4}$alkyl, or $C_{1-4}$alkoxy;

$R_{12}$ is hydrogen or methyl or ethyl or $R_{12}$ together with $L_2$ forms a $C_{5-7}$ nitrogen-containing heterocyclic ring;

$R_{13}$ is hydrogen or methyl ethyl or $R_{13}$ together with $L_4$ forms a $C_{5-7}$ nitrogen-containing heterocyclic ring;

n is 0, 1 or 2;

p is 0, 1 or 2;

q is an integer from 1 to 6

r is 0, 1 or 2;

s is 0, 1 or 2;

provided that when $R_6$ is aryl, heteroaryl, heterocyclyl, amino$C_{3-6}$alkyl, N-($C_{1-4}$alkyl)amino$C_{3-6}$alkyl or NN-(di$C_{1-4}$alkyl)amino$C_{3-6}$alkyl then $R_5$ is other than $R_6CH_2$—; and when $R_1$ is hydrogen, $R_2$ is hydrogen, $R_3$ is hydrogen, $L_1$ is hydrogen, n is 1, $R_4$ is phenyl, $R_5$ is $R_6C(O)$—, then $R_6$ cannot be 2-methyl-4-amino-butyl,

or a pharmaceutically acceptable salt, prodrug or solvate thereof.

In this specification the generic term **"alkyl"** includes both straight-chain and branched-chain alkyl groups. However references to individual alkyl groups such as "propyl" are specific for the straight-chain version only and references to individual branched-chain alkyl groups such as "isopropyl" are specific for the branched-chain version only. An analogous convention applies to other generic terms.

The term **"aryl"** refers to phenyl or naphthyl.

The term **"heteroaryl"** refers to a 5-10 membered aromatic mono or bicyclic ring containing up to 5 heteroatoms selected from nitrogen, oxygen or sulphur. Examples of 5- or 6-membered heteroaryl ring systems include imidazole, triazole, pyrazine, pyrimidine, pyridazine, pyridine, isoxazole, oxazole, isothiazole, thiazole, furan, pyrazole, 1,2,3-thiadiazole and thiophene. A 9 or 10 membered bicyclic heteroaryl ring system is an aromatic bicyclic ring system comprising a 6-membered ring fused to either a 5 membered ring or another 6 membered ring. Examples of 5/6 and 6/6 bicyclic ring systems include benzofuran, benzimidazole, benzthiophene, benzthiazole, benzisothiazole, benzoxazole, benzisoxazole, pyridoimidazole, pyrimidoimidazole, quinoline, isoquinoline, quinoxaline, quinazoline, phthalazine, cinnoline, 4-oxo-4H-1-benzopyran and naphthyridine.

The term **"heterocyclyl"** refers to a 5-10 membered non-aromatic mono or bicyclic ring containing up to 5 heteroatoms selected from nitrogen, oxygen or sulphur. Examples of 'heterocyclyl' include pyrrolinyl, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl, dihydropyridinyl and dihydropyrimidinyl

The term **"carbocyclic ring"** refers to a totally saturated or partially saturated mono, bi or tri cyclic carbon ring. Examples of carbocyclic rings are cyclopentyl, cyclohexyl, cyclopentyl, bicyclo-octane or adamantyl.

The term **"halo"** refers to fluoro, chloro, bromo and iodo.

The term **carbamoyl** refers to -C(O)$NH_2$.

The term **"warm-blooded animal"** includes human.

Examples of **$C_{1-4}$alkyl** include methyl, ethyl, propyl, isopropyl, *sec*-butyl and *tert*-butyl; examples of **$C_{1-4}$alkoxy** include methoxy, ethoxy and propoxy; examples of **$C_{1-4}$alkanoyl** include formyl, acetyl and propionyl; examples of **$C_{1-4}$alkylamino** include methylamino, ethylamino, propylamino, isopropylamino, *sec*-butylamino and *tert*-butylamino; examples of **di-($C_{1-4}$alkyl)amino** include di-methylamino, di-ethylamino and N-ethyl-N-methylamino; examples of **N-($C_{1-4}$alkyl)amino$C_{1-4}$alkyl** include N-methyl-aminomethyl and N-ethyl-aminoethyl, and examples of **NN-di($C_{1-4}$alkyl)amino$C_{1-4}$aklyl** include: NN-dimethyl- aminomethyl and N-methyl-N-ethyl aminomethyl.

Examples of suitable values for $R_1$, $R_2$ or $R_3$ include hydrogen, halo, nitro, carbamoyl, , N-($C_{1-4}$alkyl)carbamoyl, NN-(di$C_{1-4}$alkyl)carbamoyl or $C_{1-4}$alkoxycarbonyl. Preferably hydrogen, halo, nitro, carbamoyl, N-ethylcarbamoyl, NN-dimethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methoxycarbonyl or ethoxycarbonyl. More preferably hydrogen, halo or nitro. More preferably hydrogen, chloro or nitro. Most preferably either $R_1$ is halo, preferably chloro, $R_2$ is halo, preferably chloro and $R_3$ is hydrogen or $R_1$ is hydrogen, $R_2$ is nitro and $R_3$ is hydrogen.

Examples of suitable values for $R_4$ include indole, N-($C_{1-4}$alkyl) indole, $C_{5-7}$carbocyclic ring or aryl, either of which can be optionally substituted by halo, $C_{1-4}$alkyl, or $C_{1-4}$alkoxy. Preferably $R_4$ is indole, N-methylindole, cyclopentyl, cyclohexyl, phenyl or naphthyl, optionally substituted as defined above. More preferably $R_4$ is indole, N-methylindole, cyclohexyl, or phenyl, optionally substituted as defined above. More preferably $R_4$ is indole, N-methylindole, or phenyl, optionally substituted as defined above. More preferably $R_4$ is phenyl, optionally substituted as defined above. Most preferable $R_4$ is phenyl substituted with halo, preferably chloro.

Examples of suitable values for $R_5$ include hydrogen, $C_{1-4}$alkyl, $R_6CH_2-$ or $R_6C(O)-$. Preferably $R_5$ is hydrogen, methyl, $R_6CH_2-$ or $R_6C(O)-$. Most preferably $R_5$ is $R_6C(O)-$.

Examples of suitable values for $R_6$ include aryl, heteroaryl, heterocyclyl, amino-$C_{3-6}$alkyl, N-($C_{1-4}$alkyl)amino$C_{3-6}$alkyl, NN-(di$C_{1-4}$alkyl)amino$C_{3-6}$alkyl, or $R_7$. Preferably $R_6$ is aryl, heteroaryl, heterocyclyl, (NN-dimethyl)aminopropyl or $R_7$. More preferably $R_6$ is aryl,

heteroaryl, heterocyclyl or $R_7$. More preferably $R_6$ is aryl and heteroaryl. Most preferably $R_6$ is aryl, preferably phenyl.

Examples of substituents on the aryl ring systems of $R_6$ include nitro, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, halo, ($C_{1-4}$alkyl)sulfanyl. Preferably nitro, $C_{1-4}$alkyl, $C_{1-4}$alkoxy or methylsulfanyl. More preferably nitro or $C_{1-4}$alkoxy. Most preferably nitro or methoxy. More preferable substitution patterns on a phenyl group in $R_6$ are 2-nitro-4,5-dimethoxy, 2-methyl-3-nitro, 2-methoxy, 2,4-dimethyl, 4,5-dimethoxy-2-nitro or 2-methylsulfanyl. Most preferred is 2-nitro-4,5-dimethoxy.

Examples of suitable values for heteroaryl rings at $R_6$ include: furan, thiophene, pyrrole, pyrazole, isoxazole, thiazole, thiadiazole, pyridine, pyridazine, benzofuran, 4-oxo 4H-1-benzopyran. Heteroaryl ring systems with one or two heteroatoms are preferred. Heteroaryl ring systems with one heteroatom are most preferred.

Examples of suitable values for substituents on ring carbon atoms in heterocyclic rings of $R_6$ include, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, halo, hydroxy, oxo or $C_{1-4}$alkylcarbonyl.

Examples of suitable values for $R_8$ include amino, guanadino and imidazolo, any of which can be mono or di-N-substituted with $C_{1-4}$alkyl. More preferably $R_8$ is guanadino or amino, substituted as defined above. Preferably $R_8$ is N-($C_{1-4}$alkyl)amino or amino. Most preferably $R_8$ is amino.

Examples of suitable values for $R_9$ include $C_{5-7}$alkyl, a $C_{5-10}$ membered carbocyclic ring and aryl, any of which can be optionally substituted with $C_{1-4}$alkyl. Preferably $R_9$ is 3-propylbutyl, 2,2 dimethylpropyl, a $C_{5-10}$ membered carbocyclic ring, or aryl. More preferably $R_9$ is cyclohexyl, cycloheptyl, adamantyl or aryl. Even more preferably $R_9$ is cyclohexyl or aryl. Yet more preferably $R_9$ is aryl. Most preferably $R_9$ is phenyl.

Examples of suitable values for $R_{10}$ include $C_{1-4}$alkyl or a $C_{3-7}$carbocyclic ring. More preferably $R_{10}$ is a $C_{3-7}$carbocyclic ring or a branched $C_{1-4}$alkyl chain. Even more preferably $R_{10}$ is a $C_{3-7}$carbocyclic ring. Most preferably $R_{10}$ is cyclohexyl.

Examples of suitable values for $R_{11}$ include hydrogen, halo, $C_{1-4}$alkyl, or $C_{1-4}$alkoxy. More preferably $R_{11}$ is hydrogen or $C_{1-4}$alkyl. Most preferably $R_{11}$ is hydrogen.

Examples of suitable values for $R_{12}$ are hydrogen or methyl or when $R_{12}$ is —$CH_2$—, $L_2$ is hydrogen and s is 1, $R_{12}$ together with $L_2$ forms a six membered nitrogen containing ring Preferably $R_{12}$ and $L_2$ are both hydrogen.

Examples of suitable values for $R_{13}$ are hydrogen or methyl or when $R_{13}$ is —$CH_2$—, $L_4$ is hydrogen and s is 1, $R_{13}$ together with $L_4$ forms a six membered nitrogen containing ring Preferably $R_{13}$ and $L_4$ are both hydrogen.

Preferably n is 1

Preferably p is 1

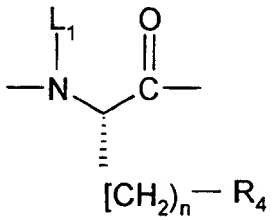
Preferably q is 2 - 4. Most preferable q is 4.

Preferably r is 1.

Preferably s is 1.

It is to be understood that, insofar as certain of the compounds of Formula (1) defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the property of inhibiting MDM2 interactions. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, inhibitory properties against MDM2 interactions may be evaluated using the standard laboratory techniques referred to hereinafter.

When $R_6$ is other than $R_7$ then the following stereo-chemistry is preferred, in the group $-N(L_1)CH((CH_2)_nR_4)CO-$, in formula (1):




Formula (X)

A particular group of compounds of the invention include for example, a compound of formula (1) wherein $R_5$ is hydrogen or $C_{1-4}$ alkyl, or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein either:

(a) $R_1$ is hydrogen; $R_2$ is nitro; $R_3$ is hydrogen; $R_4$ is indole, N-($C_{1-4}$alkyl)indole or cyclohexyl; $R_5$ is hydrogen or methyl; $L_1$ is hydrogen and n is 1 or 2; and where the optical centre represented in the Formula (X) is in the S configuration; or

(b) $R_1$ is halo; $R_2$ is halo; $R_3$ is hydrogen; $R_4$ is indole, N-($C_{1-4}$alkyl)indole or cyclohexyl; $R_5$ is hydrogen or methyl; $L_1$ is hydrogen and n is 1 or 2; and where the optical centre represented in the Formula (X) is in the S configuration.

A further preferred group of compounds of the invention include, for example a compound of formula (1) wherein $R_5$ is $R_6C(O)$– or $R_6CH_2$–, or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein either:

(a) $R_1$ is hydrogen; $R_2$ is nitro; $R_3$ is hydrogen; $R_4$ is indole; N-($C_{1-4}$alkyl)indole, halo-phenyl or cyclohexyl; $R_5$ is $R_6C(O)$ – or $R_6CH_2$–; $R_6$ is substituted phenyl; $L_1$ is hydrogen or methyl and n is 1 or 2, ; and where the optical centre represented in the Formula (X) is in the S configuration; or

(b) $R_1$ is hydrogen; $R_2$ is nitro; $R_3$ is hydrogen; $R_4$ is indole; N-($C_{1-4}$alkyl)indole; halo-phenyl or cyclohexyl, $R_5$ is $R_6C(O)$– or $R_6CH_2$–, $R_6$ is a substituted heterocycle; $L_1$ is hydrogen or methyl and n is 1 or 2, ; and wherein the optical centre represented in the Formula (X) is in the S configuration.

A further preferred group of compounds of the invention include, for example a compound of formula (1) wherein $R_5$ is $R_6C(O)$– and $R_6$ is $R_7$, or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein either:

(a) $R_1$ is hydrogen; $R_2$ is nitro; $R_3$ is hydrogen; $R_4$ is indole; N-($C_{1-4}$alkyl)indole; cyclohexyl or halo-phenyl; $R_5$ is $R_6C(O)$ –; $R_6$ is $R_7$; $R_7$ is of formula (2); $R_8$ is amino; $R_9$ is an optionally substituted aryl group; $R_{11}$ is hydrogen; $A_1$ is oxygen or a bond; n is 1 or 2; p is 1; q is 2-4 and $L_1$ and $L_2$ and $L_3$ are independently hydrogen or methyl; or

A further preferred group of compounds of the invention include, for example a compound of formula (1) wherein $R_5$ is $R_6CH_2$– and $R_6$ is $R_7$, or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

(a) $R_1$ is hydrogen; $R_2$ is nitro; $R_3$ is hydrogen; $R_4$ is indole; N-($C_{1-4}$alkyl)indole; cyclohexyl or halo-phenyl; $R_5$ is $R_6CH_2$–; $R_6$ is $R_7$, $R_7$ is of formula (3); $R_{10}$ is either a $C_{3-7}$ carbocyclic ring or a $C_{1-4}$alkyl chain; $R_{11}$ is hydrogen; $L_4$ is hydrogen or methyl and r is 1.

A more preferred compound of the invention is a compound of formula (1) wherein $R_5$ is $R_6C(O)$ – and $R_6$ is a substituted phenyl group, or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

$R_1$ is hydrogen; $R_2$ is nitro; $R_3$ is hydrogen; $R_4$ is indole; N-($C_{1-4}$alkyl)indole; or 4-chloro-phenyl; $R_5$ is $R_6C(O)$–; $R_6$ is 4,5-dimethoxy-2-nitrophenyl; $L_1$ is hydrogen or methyl; n is 1 and where the optical centre represented in the Formula (X) is in the S configuration.

A further more preferred compound of the invention is a compound of formula (1) wherein $R_5$ is $R_6C(O)$– and $R_6$ is $R_7$ and $R_7$ is of formula (2), or a pharmaceutically acceptable salts, prodrugs or solvates thereof, wherein:

$R_1$ is hydrogen; $R_2$ is nitro; $R_3$ is hydrogen; $R_4$ is indole; N-($C_{1-4}$alkyl)indole; phenyl; 4-chloro-phenyl or cyclohexyl; $R_5$ is $R_6C(O)$–; $R_6$ is $R_7$, $R_7$ is of formula (2); $R_8$ is amino;

2,5-dimethoxybenzoyl-TRP-piperazine-4-nitrophenyl;

2-benzofuroyl-TRP-piperazine-4-nitrophenyl;

N-methylpyrrole-2-carboxyl-TRP-piperazine-4-nitrophenyl;

2-bromo-5-methoxybenzoyl-TRP-piperazine-4-nitrophenyl;

thiophene-2-carboxyl-TRP-piperazine-4-nitrophenyl;

5-chlorothiophene-2-carboxyl-TRP-piperazine-4-nitrophenyl;

2-methoxy-4-nitrobenzoyl-TRP-piperazine-4-nitrophenyl;

2-furylcarbonyl-TRP-piperazine-4-nitrophenyl;

6-methylpicoliny-TRP-piperazine-4-nitrophenyl;

3-methoxy-2-nitrobenzoyl-TRP-piperazine-4-nitrophenyl;

Dimethoxynitrobenzoyl-(D)TRP-piperazine-4-nitrophenyl;

4-oxo-4H-1-benzopyran-2-caboxyl-TRP-piperazine-4-nitrophenyl;

5-nitro-2-furoyl-TRP-piperazine-4-nitrophenyl;

1,2,3-thiadiazole-4-carboxyl-TRP-piperazine-4-nitrophenyl;

Z-LYS-(NMe)PHE-TRP-piperazine-4-nitrophenyl;

cyclohexylacetyl-(D)LYS-(D)NMe-PHE-(D)TRP-piperazine-4-nitrophenyl;

adamantaneacetyl-(D)LYS-(D)NMe-PHE-(D)TRP-piperazine-4-nitrophenyl;

cycloheptanoyl-(D)LYS-(D)NMe-PHE-(D)TRP-piperazine-4-nitrophenyl;

2-propylpentanoyl-(D)LYS-(D)NMe-PHE-(D)TRP-piperazine-4-nitrophenyl;

Z-(D)NMe-LYS-(D)NMe-PHE-(D)TRP-piperazine-4-nitrophenyl;

$Me_2CHCH_2$(D,L)NME-PHE{$CH_2NH$}(D)TRP-piperazine-4-nitrophenyl;

Z-LYS-(NMe)PHE-(D)TRP-piperazine-4-nitrophenyl;

cyclohexyl-(D)LYS-(D)(NMe)PHE-(D)TRP-piperazine-4-nitrophenyl;

T-butylacetyl-(D)LYS-(D)NMePHE-(D)TRP-piperazine-4-nitrophenyl;

cyclohexyl-(D)LYS-(D)NMe-PHE-(D)PHE(4-Cl)-piperazine-dichlorophenyl; and

cyclohexyl-(D)Lys-(D)NMePhe-(D)Tyr(Et)-piperazine-4-nitrophenyl;

or a pharmaceutically acceptable salt, prodrug or solvate thereof.

Further particular compounds of the invention are:

Z-(D)(NMe)DAB-(NMe)(D)PHE-(D)TRP-piperazine-4-nitrophenyl;

Z-NMe(D)LYS-NMe(D)PHE-(D)PHE(4-Cl)-piperazine-4-nitrophenyl;

cyclohexyl-CO-(D)LYS-(D)NMe-PHE-CHA-piperazine-4-nitrophenyl;

cyclohexyl-(D)Lys-(D)(NMe)Phe-(D)Phe(4-Cl)-piperazine-4-nitrophenyl;

cyclohexyl-$CH_2$-(D,L)NMe-PHE{$CH_2NH$}(D)TRP-piperazine-4-nitrophenyl; and

cyclohexyl-(D)Lys-(D)(NMe)Phe-(D)hPhe-piperazine-4-nitrophenyl;

or a pharmaceutically acceptable salt, prodrug or solvate thereof.

A suitable pharmaceutically-acceptable salt of a compound of the Formula (1) is, for example, an acid-addition salt of a compound of the Formula (1) which is sufficiently basic, for example an acid-addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, trifluoroacetic, citric or maleic acid; or, for example a salt of a compound of the Formula (1) which is sufficiently acidic, for example an alkali or alkaline earth metal salt such as a calcium or magnesium salt, or an ammonium salt, or a salt with an organic base such as methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

Various forms of prodrugs are known in the art, for example in-vivo hydrolysable esters.

In vivo hydrolysable derivatives include, in particular, pharmaceutically acceptable derivatives that may be oxidised or reduced in the human body to produce the parent compound or esters that hydrolyse in the human body to produce the parent compound. Such esters can be identified by administering, for example, intravenously to the test animal, the compound under test and subsequently examining the test animal's body fluids. Suitable in vivo hydrolysable esters for hydroxy include acetyl and for carboxyl include, for example, alkyl esters, dialkylaminoalkoxy esters, esters of formula -C(O)-O-CH2C(O)NRa"Rb" where Ra" and Rb" are, for example, selected from hydrogen and C1-4 alkyl, and C1-6alkoxy methyl esters for example methoxymethyl, C1-6alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C3-8 cycloalkoxycarbonyloxyC1-6alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolan-2-ylmethyl esters for example 5-methyl-1,3-dioxolan-2-ylmethyl; and C1-6alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl.

a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);

b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);

c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);

d) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988); and

e) N. Kakeya, *et al.*, Chem Pharm Bull, 32, 692 (1984).

It will also be understood that certain compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms. It is to be understood that the present invention encompasses all such solvated forms which possess the property of inhibiting MDM2 interactions.

In another aspect the present invention provides a process for preparing a compound of the Formula (1) or a pharmaceutically acceptable salt, prodrug or ester thereof which process

Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Specific examples of protecting groups are given below for the sake of convenience, in which "lower" signifies that the group to which it is applied preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific examples of methods for the removal of protecting groups are given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection not specifically mentioned is of course within the scope of the invention.

A carboxy protecting group may be the residue of an ester-forming aliphatic or araliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably containing 1-20 carbon atoms).

Examples of carboxy protecting groups include straight or branched chain $C_{1-12}$alkyl groups (for example isopropyl, t-butyl); lower alkoxy lower alkyl groups (for example methoxymethyl, ethoxymethyl, isobutoxymethyl); lower aliphatic acyloxy alkyl groups, (for example acetoxymethyl, propionyloxymethyl, butyryloxymethyl, pivaloyloxymethyl); lower alkoxycarbonyloxy lower alkyl group (for example 1-methoxycarbonylethyl, 1-ethoxycarbonylethyl); phenyl lower alkyl groups (for example benzyl, p-methoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, benzhydryl and phthalidyl); tri(lower alkyl)silyl groups (for example trimethylsilyl and t-butyldimethylsilyl); tri(lower alkyl)silyl lower alkyl groups (for example trimethylsilylethyl); and $C_{2-6}$alkenyl groups (for example allyl and vinylethyl).

Methods particularly appropriate for the removal of carboxy protecting groups include for example acid-, base-, metal- or enzymically-catalysed hydrolysis.

Example of hydroxy protecting groups include lower groups (for example t-butyl), lower alkenyl groups (for example allyl); lower alkanoyl groups (for example acetyl); lower alkoxycarbonyl groups (for example t-butoxycarbonyl); lower alkenyloxycarbonyl groups (for example allyloxycarbonyl); phenyl lower alkoxycarbonyl group (for example benzoyloxycarbonyl, p-methoxybenzyloxycarbonyl, o-nitrobenzyloxycarbonyl, p-

Examples of amino protecting groups include formyl, aralkyl groups (for example benzyl and substituted benzyl, p-methoxybenzyl, nitrobenzyl and 2,4-dimethoxybenzyl, and triphenylmethyl); di-p-anisylmethyl and furylmethyl groups; lower alkoxycarbonyl (for example t-butoxycarbonyl); lower alkenyloxycarbonyl (for example allyloxycarbonyl); phenyl

[illegible] carbonyl groups (for example benzyloxycarbonyl, p-methoxybenzyloxycarbonyl

formed by the reaction of the acid and a chloroformate such as isobutyl chloroformate; an active ester, for example an ester formed by the reaction of the acid with a phenol such as pentafluorophenol, with an ester such as pentafluorophenyl trifluoroacetate or with an alcohol such as N-hydroxybenzotriazole; an acyl azide, for example an azide formed by the reaction of the acid and an azide such as diphenylphosphoryl azide; an acyl cyanide, for example a cyanide formed by the reaction of an acid and a cyanide such as diethylphosphoryl cyanide; or the product of the reaction of the acid and a carbodiimide such as dicyclohexylcarbodiimide.

The reaction between compounds of the formulae (8) and (9) is carried out under conditions known for peptide bond formation. Typically the reaction is carried out in an organic solvent such as DMF or DMA. A small amount of THF and DMSO may be added as well. The reaction is usually carried out in the presence of an activating agent such as O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) and a base, particularly an amine base, for example diisopropylethylamine. In addition 1-hydroxy-7-azabenzotriazole (HOAT) may be added as catalyst. The reaction is normally carried out in a temperature range of 0 to 80°C, preferably at around ambient temperature. 2-(1H-Benzotriazol-1yl)-1,1,3,3-tetramethyluroniumhexafluorophosphate (HBTU), may be used instead of HATU in which case 1-hydroxy-benzotriazole (HOBt) is generally used as catalyst.

The compound of the formula (8) is conveniently prepared by solid phase organic synthesis on a polymer resin. The resin is preferably one that can be removed with mild acid such as chlorotritylchloride resin. For example of other suitable polystyrene resins see the Nova Biochem Combinatorial Chemistry Catalogue February 1997.

The synthesis of a compound of the formula (8) is normally started with an amino acid which has a $-(CH_2)_nR_4$ side chain. The amino acid functional groups not taking part in the reaction are protected by various functional groups. For example, the N-terminal and side chain amino groups may be protected by using 9-fluoroenylmethoxycarbonyl (Fmoc), t-butoxycarbonyl (Boc), biphenylisopropoxycarbonyl (Bpoc), 2-[3,5-dimethoxyphenyl]propyl-2-oxycarbonyl (Ddz), adamantyloxycarbonyl (Adoc), allyloxycarbonyl (Aloc), 2,2,2-trichloroethoxycarbonyl (Troc), benzyloxycarbonyl and various substituted benzyloxycarbonyl groups. These protected groups can be cleaved when

large extent on the type of resin used. When the resin is chlorotritylchoride the preferred amino protecting group is Fmoc.

The protected amino acid is then mixed with the resin so that its reacts with the resin through its carboxy group. When the resin is chlorotrityl resin, the reaction between amino acid and resin is conventionally carried out in an organic solvent such as DMF in the presence of a base such as DIPEA. The amino-protecting group is then removed so that the $R^{5'}$ can be introduced if it is other than hydrogen. The protecting group cleavage reactions can be performed at temperatures in the range of 4°C to 40°C (preferably at or about ambient temperature) and over a period of time in the range of 10 minutes to 24 hours.

The introduction of the $R_{5'}$ group when $R_{5'}$ is of the formula $R_6C(O)$- is carried out using standard methods known for the formation of an amide bond. For example in the presence of HBTU as described above.

When $R_6$ is of the formula $R_7$ the group $R_6CO$- can gradually be built up with subsequent amide bond forming reactions. For example the group $NH(L_2)$-$CH(CH_2Ph)$-CO- may be introduced onto the amino acid attached to the resin by reacting a compound of the formula $PN(L_2)$-$CH(CH_2Ph)COOH$ (wherein P is an amino-protecting group), with the latter compound under amide bond-forming conditions. The amino-protecting group can then be removed and the resulting compound reacted with a compound of the formula $PN(L_3)CH((CH_2)_nR_8)COOH$ under similar conditions. Again the amino-protecting group can be removed and the resulting compound reacted with a compound of the formula $R_9(CH_2)_pA_1$-COOH. Alternatively the group $R_7COOH$ could be formed itself through subsequent amide-bond forming reactions and then introduced in one step onto the amino acid that is attached to the resin.

The resin is then removed, which in the case of chlorotrityl resin involves treating it with acetic acid and trifluoroethanol, to give a compound of the formula (8).

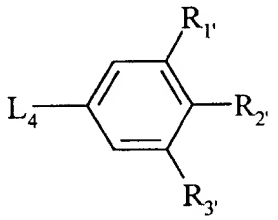
For further information on the formation of amide bonds see the procedures disclosed in "Solid Phase Peptide Synthesis : A practical approach" by Atherton and Sheppard (published by IRL press at Oxford University Press, 1989). "Solid Phase Peptide Synthesis" by Stewart and Young (published by the Pierce Chemical Company, Illinois, 1984), "Principles of Peptide Synthesis" (published by Springer-Verlag, Berlin, 1984), and a series

of books "Amino Acids, Peptides and Proteins" (volumes 1-25; volume 25 published in 1994) (published by the Royal Society of Chemistry, Cambridge, UK).

Similar reaction conditions can be used to synthesise a compound of the (8) without using a resin support.

When $R_{5'}$ is of the formula $R_6CH_2$-, a compound of the formula (8) may be prepared by reacting together a compound of the formula $R_6C(O)H$ and the appropriate amine under conditions known for the formation of a Schiff's base, followed by reduction of the Schiff's base to the methylamino group. The reaction is typically carried out in an organic solvent such as DMF or an alcohol such as methanol or ethanol. Suitable reducing agents include sodium trisacetoxyborohydride, sodium cyanoborohydride and sodium borohydride.

A compound of the formula (9) is conveniently prepared by reacting piperazine, in which one nitrogen is protected, with a group of the formula :




wherein $L_4$ is a leaving group and $R_{1'}$ - $R_{3'}$ are as hereinabove defined. Preferably the leaving group is chloro. The reaction is generally carried out in an inert organic solvent such as toluene or methylformamide, in the presence of an organic base such as triethylamine or DBU, in a temperature range of 80-200°C, preferably at reflux.

Optional substituents in a compound of the formula (1) or (7) or intermediates in their preparation may be converted into other optional substituents. For example an hydroxy group could be alkylated to a methoxy group.

Various substituents may be introduced into compounds of the formulae (1) or (7) and intermediates in this preparation, when appropriate, using standard methods known in the art. For example, an acyl group or alkyl group may be introduced into an activated benzene ring using Friedel-Crafts reactions, a nitro group by nitration with concentrated nitric acid and concentrated sulphuric acid and bromination with bromine or tetra(n-butyl)ammonium tribromide.

It will be appreciated that, in certain steps in the reaction sequence to compounds of the formula (1), it will be necessary to protect certain functional groups in intermediates in

order to prevent side reactions. Deprotection may be carried out at a convenient stage in the reaction sequence once protection is no longer required.

In order to use a compound of the Formula (1), or a pharmaceutically-acceptable salt or in vivo cleavable ester thereof, for the therapeutic treatment (including prophylactic treatment) of mammals including humans, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

According to this aspect of the invention there is provided a pharmaceutical composition which comprises an amide derivative of the Formula (1), or a pharmaceutically-acceptable or in vivo cleavable ester thereof, as defined herein before in association with a pharmaceutically-acceptable diluent or carrier.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Suitable pharmaceutically-acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

Suppository formulations may be prepared by mixing the active ingredient with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

Topical formulations, such as creams, ointments, gels and aqueous or oily solutions or suspensions, may generally be obtained by formulating an active ingredient with a conventional, topically acceptable, vehicle or diluent using conventional procedures well known in the art.

Compositions for administration by insufflation may be in the form of a finely divided powder containing particles of average diameter of, for example, 30μm or much less, the powder itself comprising either active ingredient alone or diluted with one or more physiologically acceptable carriers such as lactose. The powder for insufflation is then conveniently retained in a capsule containing, for example, 1 to 50mg of active ingredient for use with a turbo-inhaler device, such as is used for insufflation of the known agent sodium

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on Formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral

The compounds of this invention may be used in combination with other drugs and therapies used in the treatment of disease states which would benefit from the inhibition of the interaction of p53 and MDM2. For example, the compounds of the Formula (1) could be used in combination with drugs and therapies used in the treatment of cancers, including, but not limited to, breast cancer, sarcomas, osteosarcoma, testicular cancer or oesophageal cancer.

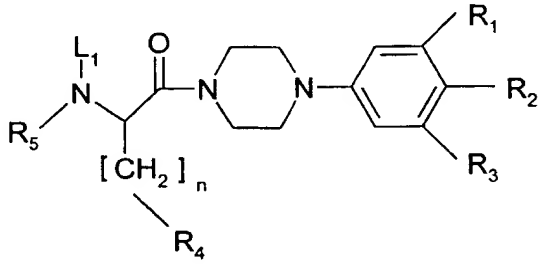
If formulated as a fixed dose such combination products employ the compounds of this invention within the dosage range described herein and the other pharmaceutically-active agent within its approved dosage range. Sequential use is contemplated when a combination formulation is inappropriate.

Although the compounds of the Formula (1) are primarily of value as therapeutic agents for use in warm-blooded animals (including man), they are also useful whenever it is required to inhibit the interaction of p53 and MDM2. Thus, they are useful as pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents.

In a further aspect of the invention there is provided a method of probing the biochemistry of MDM2 interactions using a compound of formula (1).

In a further aspect of the invention there is provided for use in the treatment of a warm-blooded animal, by therapy, a compound of formula (1), or a pharmaceutically acceptable salt, prodrug or solvate thereof as herein defined.

In a further aspect of the invention there is provided a method of treating cancers which comprises administering to a warm-blooded animal an effective amount of a compound of formula (4),




formula (4)

wherein :

$L_1$ is hydrogen or methyl;

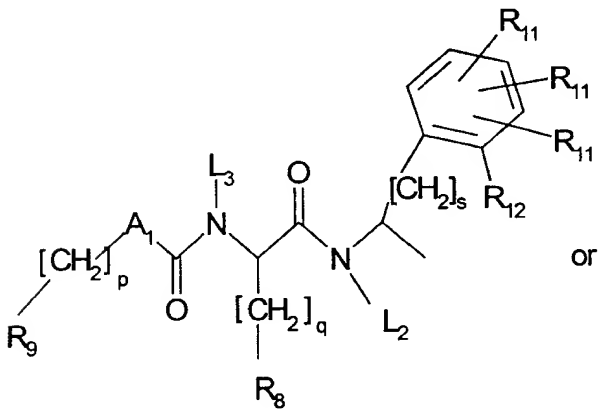
$R_1$ and $R_2$ and $R_3$ are each independently hydrogen, halo, nitro, cyano, carbamoyl, N-($C_{1-4}$alkyl)carbamoyl, NN-(di$C_{1-4}$alkyl)carbamoyl or $C_{1-4}$alkoxycarbonyl;

$R_4$ is indole, N-($C_{1-4}$ alkyl) indole, $C_{5-7}$carbocyclic ring or aryl, any of which can be optionally substituted on ring carbon atoms with up to three substituents each independently selected from halo, $C_{1-4}$alkyl, or $C_{1-4}$alkoxy;

$R_5$ is hydrogen, $C_{1-4}$alkyl, $R_6CH_2-$ or $R_6C(O)-$;

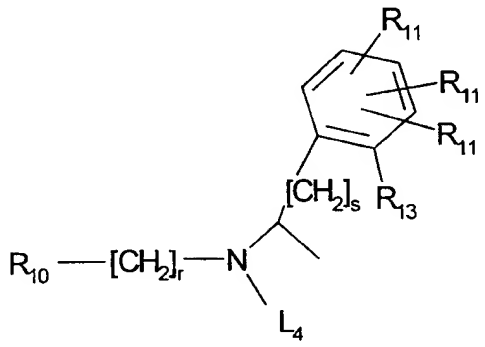
$R_6$ is aryl, heteroaryl, heterocyclyl, amino$C_{3-6}$alkyl, N-($C_{1-4}$alkyl)amino$C_{3-6}$alkyl, NN-(di$C_{1-4}$alkyl)amino$C_{3-6}$alkyl, or $R_7$; wherein the aryl, heteroaryl or heterocyclyl rings may be optionally substituted with up to three substituents independently selected from nitro, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, halo, ($C_{1-4}$alkyl)sulfanyl, $C_{1-4}$ alkoxycarbonyl, N-($C_{1-4}$ alkyl)carbamoyl, NN-(di$C_{1-4}$ alkyl)carbamoyl, N-($C_{1-4}$ alkyl)amino or NN-(di$C_{1-4}$ alkyl)amino;

wherein $R_7$ is either a group of formula (5) of formula (6):



Formula (5)

or



Formula (6)

wherein:

$L_2$, $L_3$ and $L_4$ are each independently hydrogen or methyl;

$R_8$ is amino, guanadino, imidazolo, any of which can be mono or di-N-substituted with $C_{1-4}$alkyl;

$A_1$ is oxygen or a direct bond;

$R_9$ is a $C_{5-8}$ membered mono-carbocyclic ring, a $C_{6-10}$ membered bi-carbocyclic ring, $C_{8-12}$ membered tri-carbocyclic ring, $C_{5-7}$alkyl or aryl, any of which can be optionally mono, bi or tri substituted by $C_{1-4}$ alkyl;

$R_{10}$ is $C_{1-6}$alkyl or a $C_{3-8}$mono-carbocyclic ring;

$R_{11}$ is hydrogen, halo, $C_{1-4}$alkyl, or $C_{1-4}$alkoxy;

$R_{12}$ is hydrogen or methyl or ethyl or $R_{12}$ together with $L_2$ forms a $C_{5-7}$ nitrogen-containing heterocyclic ring;

$R_{13}$ is hydrogen or methyl ethyl or $R_{13}$ together with $L_4$ forms a $C_{5-7}$ nitrogen-containing heterocyclic ring;

n is 0, 1 or 2;

p is 0, 1 or 2;

q is an integer from 1 to 6

r is 0, 1 or 2;

s is 0, 1 or 2;

provided that when $R_6$ is aryl, heteroaryl, heterocyclyl, amino$C_{3-6}$alkyl, N-($C_{1-4}$alkyl)amino$C_{3-6}$alkyl or NN-(di$C_{1-4}$alkyl)amino$C_{3-6}$alkyl then $R_5$ is other than $R_6CH_2$—; or a pharmaceutically acceptable salt, prodrug or solvate thereof.

In a further aspect of the invention there is provided a method of treating cancers, mediated by wild type or altered MDM2, which comprises administering to a warm-blooded animal an effective amount of a compound of formula (4), or a pharmaceutically acceptable salt, prodrug or solvate thereof as herein defined.

In a further aspect of the invention there is provided the use of a compound of formula (4) or a pharmaceutically acceptable salt, prodrug or solvate thereof as herein defined, in the manufacture of a medicament for use in the treatment of cancer.

In a further aspect of the invention there is provided the use of a compound of formula (4) or a pharmaceutically acceptable salt, prodrug or solvate thereof as herein defined, in the manufacture of a medicament for use in the treatment of cancer, mediated by wild type or altered MDM2.

In a further aspect of the invention there is provided the use of a compound of formula (4) or a pharmaceutically acceptable salt, prodrug or solvate thereof as herein defined in the manufacture of a medicament for the treatment of cancer in a warm-blooded animal.

In a further aspect of the invention there is provided the use of a compound of formula (4) or a pharmaceutically acceptable salt, prodrug or solvate thereof as herein defined

in the manufacture of a medicament for the treatment of cancers, mediated by wild-type or altered MDM2, in a warm-blooded animal.

In a further aspect of the invention there is provided a pharmaceutical composition comprising a compound of formula (4), or a pharmaceutically acceptable salt, prodrug or solvate thereof as herein defined, in admixture with a pharmaceutically-acceptable diluent or carrier for the treatment of cancer in a warm-blooded animal.

In a further aspect of the invention there is provided a pharmaceutical composition comprising a compound of formula (4), or a pharmaceutically acceptable salt, prodrug or solvate thereof, in admixture with a pharmaceutically-acceptable diluent or carrier for the treatment of cancer, mediated by wild-type or altered MDM2, in a warm-blooded animal.

The following biological assay provides a method of measuring the inhibition of the interaction of p53 with MDM2.

Biological Assays

**Measurement of the inhibition of p53 / MDM2 interaction**

The inhibition of the p53 / MDM2 interaction by compounds was measured using a modified ELISA assay using a histidine tagged MDM2 [MDM2 (1-118) 6 his], a p53 GST fusion protein (GST-p53) and a nickel chelate - alkaline phosphatase (NTA-AP).

The human MDM2 N-terminal fragment encompassing amino acids 1-118 and immediately followed by a C-terminal 6-histidine tag sequence and then a stop codon was generated by PCR from a human placental cDNA library. The PCR product was initially cloned into pCR2.1 vector (Invitrogen) following the manufacturers protocol. DNA sequencing confirmed a MDM fragment sequence identical to that to of published MDM2 (EMBL accession no. Z12020). The MDM2-6His fragment was then suncloned into pTB375

The background vector for generation of pTB375 was pZEN0042 (pICI0042), described fully in UK patent application GB 2253852. Briefly, pZEN0042 contains the tetA/tetR inducible tetracycline resistance sequence from plasmid RP4 and the cer stability sequence from plasmid pKS492 in a pAT153 derived background. pTB375 was generated by the addition of an expression cassette consisting of the T7 gene 10 promoter, multiple cloning site and T7 gene 10 termination sequence. In addition, a terminator sequence designed to reduce transcriptional readthrough from the background vector was included upstream of the expression cassette.

A DNA fragment encoding aa1-50 of p53 followed by a stop codon was generated by PCR using vector pHp53B (ATCC clone no. 57255) as template. The PCR product was initially cloned into pCR2.1 vector (Invitrogen) following the manufacturers protocol. DNA sequencing confirmed a p53 sequence identical to that to of published p53 (EMBL accession no. X04269).

The p53 fragment was then subcloned into pGEX-4T1 E coli expression vector (Pharmacia) to produce the expression vector pGEX-4T1-p53(1-50) clone no. 7.

The sequence of the expression vector at the junction of the GST and p53 sequences was as follows:

GST seq.....CTG GTT CCG CGT GGA TCC ATG.....

(ATG is aa1 of p53, GGA TCC is the conserved BamHI cloning site)

Expression grows were perfomed in E.coli strain DH5alpha and expression of the recombinant protein was induced by addition of IPTG. GST-p53(1-50) was purified using glutathione -sepharose beads (Pharmacia). The procedures used for expressing the GST fusion protein are therefore analogous procedures to those disclosed by J. Han *et al.*, Journal of Biological Chemistry, 1996, 271, 2886-2891.

In the assay the following solutions were used:

Stock GST-p53 (6.1mg/ml / ~200uM) diluted 2706 fold using $H_2O$;

Stock MDM2-6His (1.1mg/ml, ~70uM) diluted 933 fold using $H_2O$;

Stock NTA-AP was made by reconstituting lyophilised Ni-NTA-AP (Qiagen 34510 - 200µg) in 500ul distilled water and stored as frozen aliquots . It was frehly diluted 1:1000 using phosphate buffered saline (PBS) for use in the assay;

PNPP buffer - 100mM Tris HCl, pH 9.5, 100mM NaCl, 5mM $MgCl_2$;

2.5mM Phosphatase substrate (Sigma 104 phosphatase substrate) was dissolved in PNPP buffer approximately 20 minutes prior to use; it was kept in the dark;

Double distilled water was used throughout the assay.

100µl of 75nM GST-p53 was added per well to a 96 well plate (Nunc Maxisorp) and the plate left at 4°C overnight. Next day the fluid in the wells was removed and discarded and 100µl 0.2% bovine serum albumin (BSA) in PBS was added to each well and left at room temperature for 1 hour. The fluid was then removed and discarded and each well was washed twice with 0.1% Tween in PBS. After removing and discarding the second tween/PBS wash, 10µl of compound was added to each well, followed by 90µl 75nM MDM2-6His. The plate was then incubated at room temperature for 1.5 hours. After this time the fluid from each well was removed and discarded and each well was washed three times with 280µl Tween/PBS. After removing and discarding the final wash, 100µl NTA-AP was added to each well and the plate incubated at room temperature for 1.5 hours. After this time the fluid from each well was removed and discarded and each well was washed three times with 280µl Tween/PBS. Next ,100µl phosphatase substrate in PNPP buffer was added and the plate left for 1-2 hours at 30°C. The optical density of each well was measured at 405nm.

Compounds were tested at a final concentration between 0 and 100µM. Stock solutions of compound were made at 30µM in DMSO, dilutions were made in $H_2O$.

Although the pharmacological properties of the compounds of the Formula (1) vary with structural change as expected, in general compounds of the Formula (1) possess an $IC_{50}$ in the above test in the range, for example, 0.03 to 200µM. Thus by way of example the compound of Example 9 herein has an $IC_{50}$ of approximately 4µM.

The invention will now be illustrated by the following non-limiting Examples in which, unless otherwise stated:-

(i) concentrations and evaporations were carried out by rotary evaporation in vacuo;

(ii) operations were carried out at room temperature, that is in the range 18-26°C;

(iii) yields, when given, are intended for the assistance of the reader only and are not necessarily the maximum attainable by diligent process development;

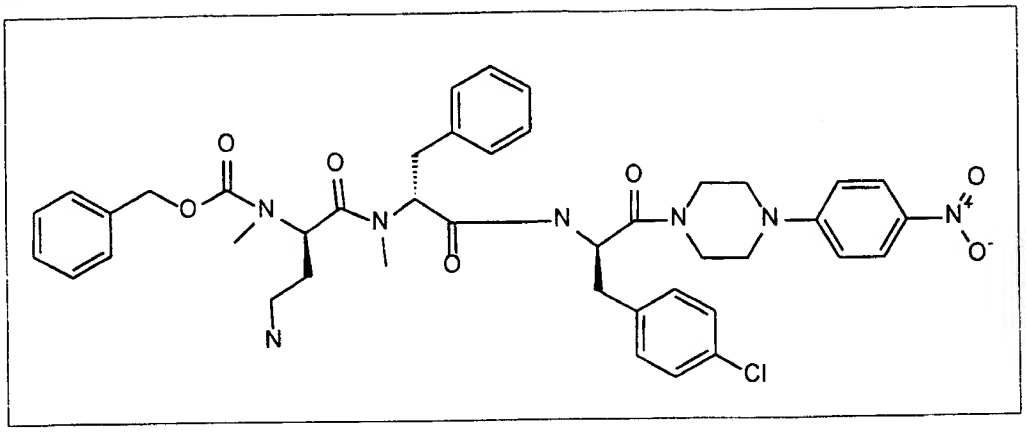
(iv) the following abbreviations are used:

BOC = tert-butoxycarbonyl; Cha = is an amino acid residue with a cyclohexylmethyl side chain; Dab = is an amino acid residue with a 2-aminoethyl side chain; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DMF = N,N-dimethylformamide; HOBt = 1-hydroxy-benzotriazole; Met = methionine; Fmoc = 9-fluorenylmethyloxycarbonyl; THF = tetrahydrofuran; DMSO = dimethylsulfoxide; HATU = O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; HBTU = 2-(1H-benzotriazol-1yl)-1,1,3,3-tetramethyluroniumhexafluorophosphate; HOAT = 1-hydroxy-7-azabenzotriazole; DIPEA = diisopropylethylamine; TFA = trifluoroacetic acid; HPLC = high pressure liquid chromatography; TCE = trichloroethane; RP-HPLC = reverse phase high pressure liquid chromatography (which unless otherwise stated was carried out on a Vydac C18 column 218TP54, 4.6 x 250 mm); and Z = benzyloxycarbonyl;

(v) flash chromatography and chromatography on silica were performed on Merck Kieselgel 60 (Art No. 9385) obtained from E Merck, Darmstadt, Germany; and

(vi) $^1$H NMR spectra were determined at 200 Mhz in $CDCL_3$ or $d_6$-dimethylsulphoxide ($d_6$-DMSO) using tetramethylsilane (TMS) as an internal standard, and are expressed as chemical shift (delta) values in parts per million relative to TMS using conventional abbreviations for designation of major peaks: s, singlet; m, multiplet; t, triplet; br, broad, d, doublet.

**Example 1**



**Z-NMe(D)Dab-NMe(D)Phe-(D)Phe(4-C1)-piperazine-4-nitrophenyl**

Z-NMe(D)Dab(BOC)-NMe(D)Phe-(D)Phe(4-Cl)-OH (assuming 0.25mmol) was dissolved in DMF(1ml). 4-Nitrophenyl-piperazine (1.2eq, 15.5mg), HATU(1eq, 19mg) and DIPEA(3.6eq, 157µl) were added and the mixture was stirred overnight at ambient temperature. RP-HPLC indicated that the reaction was 50% complete. It was evaporated to dryness and the BOC group removed by treatment with TFA/TIPS/water 10:1:1 (6ml, 5:0.5:0.5).

The resulting peptide was purified by preparative RP-HPLC ( Vydac C18 218TP1022 column eluting with an acetonitrile - water system containing 0.1%TFA (5 to 60% acetonitrile over 80 minutes), flow rate 12ml/min). The fractions containing the product were combined and lyophilised to give Z-NMe(D)Dab-NMe(D)Phe-(D)Phe(4-Cl)-piperazine-4-nitrophenyl, 6.5mg(3.25% yield).

The product was characterised by HPLC and mass spectrometry:

RP- HPLC Vydac C18 218TP54 4.6x250mm column eluting at 1.2ml/min in water and acetonitrile containing 0.1%TFA (30-70% acetonitrile over 20 minutes) retention time 15.27 minutes, no detectable impurities, mass spectrometry, m/e (positive electrospray, (ES+)) 798.5, 799.1, 800.5 (MH+).

The starting material was prepared by solid phase synthesis starting with Wang Resin in a Bond Elut (Varian 25ml, fitted with a filter in the bottom):

Wang Resin(Novabiochem,1.28g) was stirred in dichloromethane (15ml)with MSNT (ref. Birgt Blankeymeyer-Menge, *Tet Lett.* 1990, **31,** 1701)( 2mmol, 592mg) and Fmoc-Phe(4-Cl)-OH (2mmol, 845mg) for 45 minutes. The resin was washed with dichloromethane

(3x10ml) then methanol (3x10ml). The resin was dried *in vacuo* at 40°C overnight. Weight gain indicated a loading of 0.59mmol/g for Fmoc(D)Phe(4-Cl)-Wang Resin.

The Fmoc group was removed with 20% piperidine in DMF (3x10min , 10 ml each time) to give H-(D)Phe(4-Cl)-Wang Resin.

H-(D)Phe(4-Cl) -Wang Resin (423mg ~0.25mmol) was placed in another Bond Elut (15ml). FmocNMe(D)Phe-OH(3eq, 301mg) was dissolved in DMF(1.5ml), HBTU (3eq, 284mg) and DIPEA (9eq) were added. After 5 minutes this mixture was added to the resin and stirred for 1- 1.5h at ambient temperature. The resin was then washed with DMF (3x10ml).

The Fmoc group was removed with 20% piperidine in DMF (3x10min , 10 ml each time) to give NMe(D)Phe-(D)Phe(4-Cl)-Wang Resin.

Fmoc-Dab(BOC)-OH (3eq, 340mg) was coupled to the N-terminus of NMe(D)Phe(D)-Phe(4-Cl)-Wang Resin using a similar method to the coupling of Fmoc-Phe(4-Cl)-OH, except HATU(3eq, 285mg) was used instead of HBTU, to give Fmoc-Dab(BOC)NMe(D)Phe-(D)Phe(4-Cl)-Wang Resin.

The Fmoc group was removed with 20% piperidine in DMF (3x10min , 10 ml each time) to give Dab(BOC)-NMe(D)Phe-(D)Phe(4-Cl)-Wang Resin.

The resin was washed with DMF(3x10ml) and suspended in dichloromethane (5ml) to which was added 2-nitrobenzenesulfonyl chloride (3eq, 166mg) and 2,4,6-collidine (5eq, 165µl). After 2 hours the resin was washed with dichloromethane (3x5ml) and suspended in DMF (5ml). To this was added MTBD (ref. Miller, *J. Am. Chem. Soc.*, **1997,** 119,2301)(2-4eq, 100µl) and methyl-4-nitrobenzene sulfonate (3-5eq, 200mg). After 30 minutes the resin was washed with DMF (3x5ml) and the resin suspended in DMF (5ml). DBU (5eq, 187µl) and mercaptoethanol (10eq, 175µl) were added and after 30 minutes the resin was washed with DMF (5x10ml).

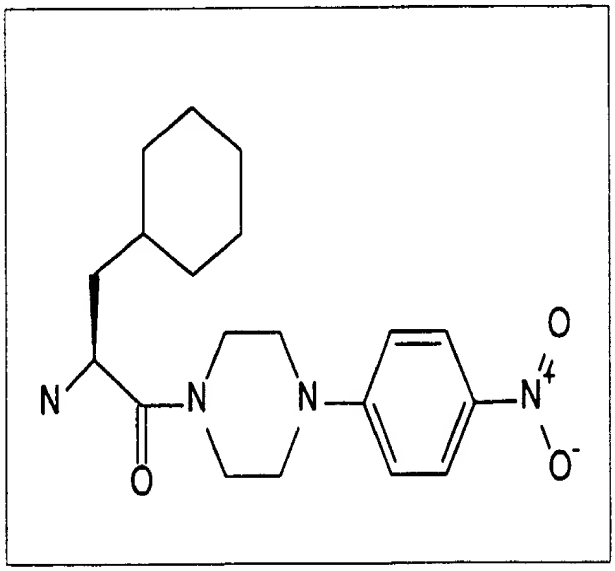
The resin was wet with DMF (1-2ml) and benzoyl chloroformate (4eq, 170mg) and DIPEA (12eq, 0.52ml) added. After 1.5 hours the resin was washed with DMF (3x10ml) and then methanol ( 3x10ml). The resin was dried once more *in vacuo* overnight to give Z-NMe-(D)Dab-NMe(D)Phe-(D)Phe(4-Cl)-Wang resin.

Z-NMeDab-NMe(D)Phe-(D)Phe(4-Cl)-OH was cleaved from the resin by addition of TFA:TIPS:water (10:1:1, 12ml). The resin was filtered and washed thoroughly with

TFA(3x5ml) and the solution was evaporated to dryness and lyopholised from water to yield an oil.

The BOC group was reintroduced on to Z-NMeDab-NMe(D)Phe-(D)Phe(4-Cl)-OH (assuming 0.25mmol) by treating it with di t-butyl-dicarbonate(4eq) in DMF (1-2ml) and DIPEA(12ml). RP-HPLC indicated that the reaction was complete after 1h (Vydac C18 218TP54 4.6x250mm acetonitrile - water system containing 0.1%TFA, 10-90% acetonitrile over 20minutes, flow 1.2ml/min). The solution was evaporated to dryness and washed with 1M Citric acid (2x5ml) then hexane(2x5ml). It was dried *in vacuo* overnight in the presence of phosphorous pentoxide to give Z-NMe(D)Dab(BOC)-NMe(D)Phe-(D)Phe(4-Cl)-OH as an oil.

**Example 2**




**Cyclohexylalanine-piperazine-4-nitrophenyl**

Fmoc-cyclohexylalanine (39mg, 0.1mmol) was dissolved in DMF (1ml) and piperazine-4-nitrobenzene (25mg, 1.2eq) HATU (1.2eq, 47mg) and DIPEA (3.6eq, 63µl) were added and

Fractions containg product were combined and lyopholised to yield cyclohexylalanine-piperazine-4-nitrobenzene (36mg, quantitative yield).

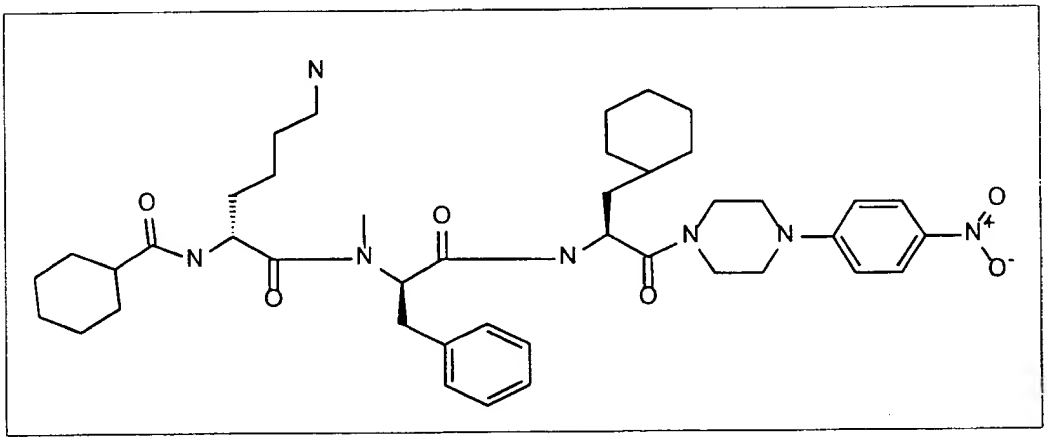
The product was characterised by HPLC, mass spectrometry and 1H NMR:

RP-HPLC Vydac C18 218TP54 column 4.6x250mm eluting with acetonitrile and water containing 0.1%TFA, using a 10-50% acetonitrile gradient over 20 minutes, flow rate 1.2ml/min , retention time17.61 minutes with no detectable impurities.

Mass Spectrometry m/e (Electrospray(ES+)) 361.5 MH+

$^1$H-NMR(DMSO): 1.2(m, 3H), 1.6(m, 8H), 3.6(m, 10H), 4.4(m, 1H) 7.0(d, 2H), 8.1(m, 4H).

**Example 3**



**Cyclohexyl-CO-(D)Lys-NMe(D)Phe-Cha-piperazine-4-nitrophenyl**

Cyclohexyl-CO-(D)Lys(BOC)-NMe(D)Phe-Cha-resin (0.05mmol) was dissolved in DMF (1ml) and activated with HATU (1eq, 19mg), DIPEA (3eq, 26µl) and coupled to N-(4-nitrophenyl)piperazine (1.5eq, 15.5mg) overnight. RP-HPLC indicated that the reaction was complete (VYDAC 201HS54 column, flow rate 1.2ml/min water-acetonitrile gradient containing 0.1% TFA using a 10-90% acetonitrile gradient over 20 minutes).

The solution was evaporated to dryness and treated with a mixture of TFA/TIPS/water (12ml, 10:1:1) for 30 minutes. After further evaporation to dryness the product was taken up in 50% acetonitrile/water and purified by preparative RP-HPLC (Dynamax 83-221 C 60Angstrom column 12ml/min in a water- acetonitrile system containing 0.1% TFA, using a 30-70% acetonitrile gradient over 1hour. The fractions containing product were combined and lyophilised to give cyclohexyl-CO-(D)Lys-NMe(D)Phe-Cha-piperazine-4-nitrobenzene (30mg, 79% yield).

The product was characterised by HPLC and mass spectrometry.

RP-HPLC Vydac C18 column, 218TP54, 4.6x250mm eluting with water- acetonitrile containing 0.1%TFA, using a 20-60% acetonitrile gradient over 20 minutes, flow 1.2ml/min indicates purity of 99.3%, retention time 15.11 minutes. Mass spectrometry m/e ( Positive electrospray (ES+)) 759.7, 761, 761.9 (MH+)

The starting material was synthesised on an ABI 430 Automated Peptide Synthesiser starting from 2-chlorotritylchloride resin( Alexis, 188mg, 0.25mmol).

Fmoc Cha-OH (1mmol each time) was double coupled to the chlorotrityl chloride resin in the standard way using, dichloromethane (5ml each time) with diisopropylamine (2eq, 348µl each time) to give Fmoc-Cha-resin.

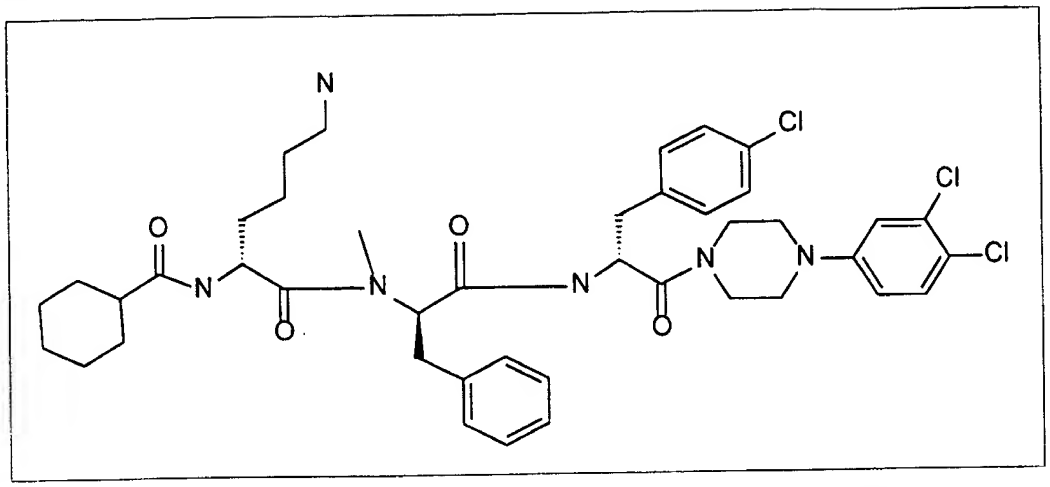
Fmoc was removed using a similar method to that used in example 1 but using 5ml of piperidine in DMF each time.

Fmoc-NMe(D)Phe-OH (1mmol, 401mg) was coupled to Cha-resin using HBTU (1mmol, 379mg) and HOBT (1mmol,135mg) in DMF with DIPEA (2mmol, 378µl), for 1 hour at ambient temperature. The resin was washed thoroughly with dichloromethane (5x5ml) to give Fmoc-(D)NMe Ph-Cha-resin. Fmoc was removed using a similar method to that described in example 1.

Fmoc-Lys(BOC)-OH (1mmol, 468mg) was coupled to NMe(D)Ph-Cha-resin using HATU (1mmol, 380mg) in DMF with DIPEA (2mmol, 348µl), at ambient temperature for 1 hour. The resin was washed thoroughly with DMF (5x5ml). Fmoc was removed using a similar method to that described in example 1.

Cyclohexanecarboxylic acid (1mmol, 128mg) was coupled to the peptide resin using a similar method to that used for the incorporation of Fmoc-NMe(D)Phe-OH. The peptide was cleaved from the resin using a mixture of acetic acid, trichloroethane and dichloromethane(14ml 2:2:10) for 2h. The resin was filtered and washed thoroughly with acetic acid:dichloromethane (1:4). The filtrate was evaporated to dryness and taken up in water and finally lyophilised to give cyclohexyl-CO-(D) Lys-(BOC)NMe(D)Phe-Cha-resin.

**Example 4**



**Cyclohexyl-(D)LysNMe(D)Phe-(D)Phe(4-Cl)-piperazine-3,4-dichlorophenyl**

HATU (39mg, 0.1mmol) was added to a stirred solution of cyclohexyl-(D)Lys(BOC)-NMe(D)Phe(4-Cl)-OH (70mg, 0.1mmol), diisopropylethylamine (70µl, 4 equivalents) and dichlorophenyl piperazine (24mg, 0.1mmol) in DMF (4ml). After 1 hour at ambient temperature, RP-HPLC indicated that most of the acid had been consumed and a new peak, retention time 30.58 minutes (column and gradient as described at the bottom of this example) had been formed. The solvent was evaporated in vacuo, and the residue was dissolved in a mixture of TFA (9ml), water (1ml) and triethylsilane (0.3ml). After 1 hour at ambient temperature, excess reagents were evaporated and the crude product now dissolved in acetonitrile (2ml) and water (2ml) for analytical and preparative RP-HPLC. The crude product was purified using preparative RP-HPLC (Dynamax C18, 1 inch internal diameter), using a gradient of acetonitrile-water containing 0.1% TFA (20-90% acetonitrile) over 60 minutes at a flow-rate of 12ml/minute. Fractions which contained the title product (eluting at 50 minutes) were combined and freeze-dried. Yield 69.6mg.

The product was characterised by HPLC, mass spectroscopy and amino-acid analysis.

RP-HPLC Vydac C18 column, 201HS54, 4.6x250mm, eluting with acetonitrile and water containing 0.1% TFA, using a 20-60% acetonitrile gradient over 30 minutes, flow rate 1.2ml/minute, retention time 22.15 minutes, no detectable impurities; mass spectrometry, m/e (positive electrospray (ES+)) 811.4 (MH+); amino acid analysis (acid hydrolysis over 24 hours using a solution of 6N HCl containing 1% phenol at 130°C) gave Phe(4-Cl) 0.84, Lys 1.00.

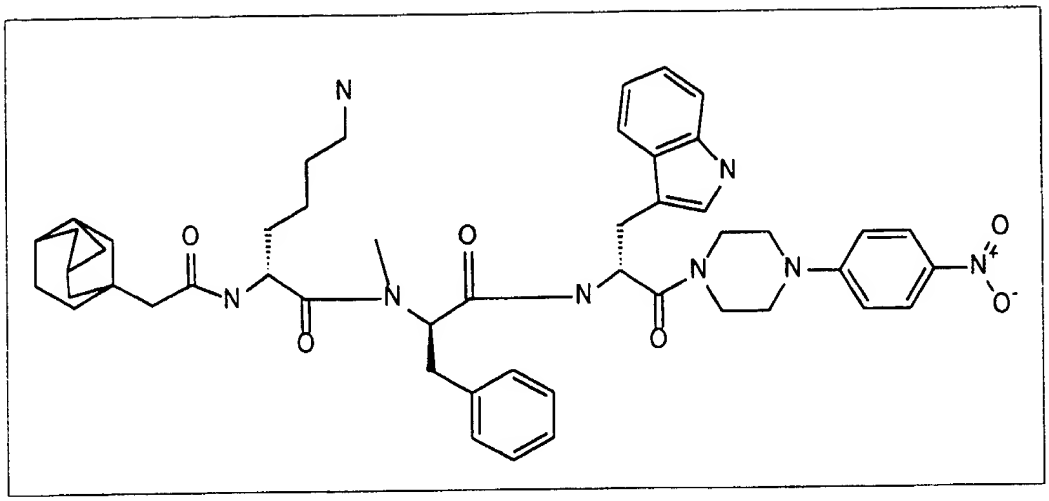
The starting material was prepared as follows:

Fmoc-(D)Phe(4-Cl)-OH (844mg, 2mmol) was coupled to 2-chlorotritylchloride resin (Alexis, 0.75g, 1mmol) in the presence of diisopropylethylamine (2mmol 0.35ml) in DMF (8ml) by an automated procedure on an Applied Biosystems 430A peptide synthesiser. After 1 hour at ambient temperature, the resin was filtered and washed with DMF. After deprotection with 20% piperidine in DMF (two treatments with 15ml), the resin was thoroughly washed with DMF (5x10ml). Fmoc-NMe(D)Phe-OH (803mg, 2mmol) was coupled to the resin-bound H-(D)Phe(4-Cl) by the standard HBTU/HOBt chemistry similar to that used in example 3. After extensive washing with DMF, the deprotection procedure described above was repeated to give H-NMe(D)Phe-(D)Phe(4-Cl)-resin. Fmoc-(D)Lys(BOC)-OH (938mg, 2mmol) was coupled by the HATU procedure (see J Chem Soc. Chem Comm. 1994, 201). After 1 hour at ambient temperature the resin as filtered and washed with DMF. After deprotection and extensive washing with DMF, cyclohexane carboxylic acid (256mg, 2mmol) was coupled by standard HBTU/HOBt chemistry similar to that described above to the resin bound tripeptide to give cyclohexyl-(D)Lys(BOC)-NMe(D)Phe-(D)Phe(4-Cl) on the resin. The peptide resin was collected and washed with methanol and dried, in vacuo, at 50°C. Yield 1.337g (gain 587mg).

The peptide was cleaved from the resin using a mixture of dichloromethane (20ml), trifluoroethanol (4ml) and acetic acid (4ml) at ambient temperature. After 2 hours, the mixture was filtered and the resin was washed with a mixture of acetic acid in dichloromethane (5%) (5x20ml). The combined filtrate and washes were evaporated to dryness and the residue was dissolved in a mixture of acetonitrile (100ml) and water (50ml) for analytical RP-HPLC and lyophilisation. Yield 604mg (86%).

RP-HPLC Vydac C18 column, 201HS54, 4.6x250mm, eluting with acetonitrile and water containing 0.1% TFA, using a 20-80% acetonitrile gradient over 40 minutes, flow rate 1.2ml/minute, indicated 100% purity, retention time 22.05 minutes no detectable impurities.

**Example 5**



**Adamantylacetyl-(D)Lys-NMe(D)Phe-(D)Trp-piperazine-4-nitrophenyl**

Adamantylacetyl-(D)Lys(BOC)-NMe(D)Phe-(D)Trp-OH (77mg, 0.1mmol) was coupled to 4-(nitrophenzyl)piperazine (21mg, 0.1mmol) by a similar procedure to that described in example 4. Analytical RP-HPLC (column and conditions as for the protected peptide acid below) indicated almost complete conversion to the amide, retention time 23.39 minutes. After deprotection with TFA and scavengers (water and triisopropylsilane), the crude product was purified by preparative RP-HPLC (Dynamax C18, 1 inch internal diameter using a gradient of acetonitrile-water containing 0.1% TFA (20-70% acetonitrile) over 60 minutes at a flow rate of 12ml/minute. Fractions which contained the pure title product (eluting at 55 minutes) were combined and freeze dried. Yield 43mg.

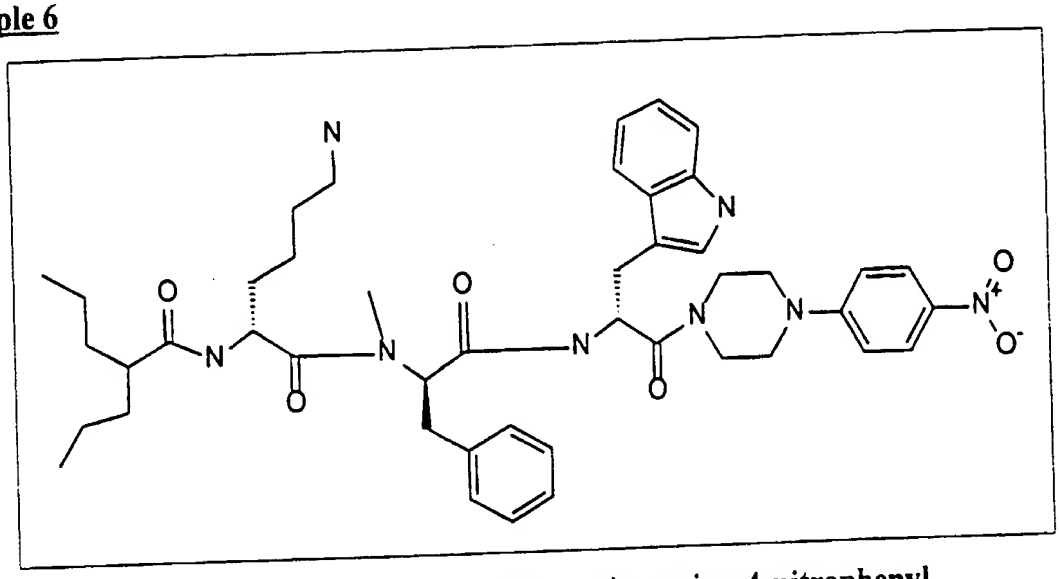
The product was characterised by HPLC and mass spectroscopy. RP-HPLC (column and conditions exactly as for previous example) indicated 100% purity, retention time 19.66 minutes; mass spectrometry m/e (positive electrospray ($ES^+$)) 859.6 ($MH^+$).

The starting material was prepared as follows:

Adamantylacetyl-(D)Lys(BOC)-NMe(D)Phe-(D)Trp-OH was prepared by a similar method to that described in example 4, but on a smaller scale (0.4mmol). Yield 186mg (60%).

RP-HPLC Vydac C18 column, 201HS54, 4.6x250mm, eluting with acetonitrile and

**Example 6**



**2-Propylpentanoyl-(D)Lys-NMe(D)Phe-(D)Trp-piperazine-4-nitrophenyl**

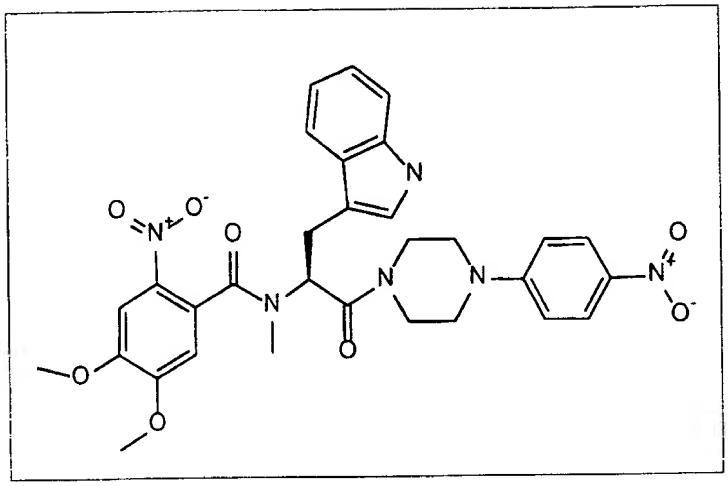
This title compound was prepared using a similar method to that of example 4. The protected peptide amide had a retention time of 22 minutes on RP-HPLC (column and conditions as for the protected peptide acid below). After deprotection with TFA and scavengers, preparative RP-HPLC was performed exactly as described for the proceeding example and fractions which contained product (eluting at 40 minutes) were combined and freeze dried. Yield 93mg.

RP-HPLC (column and conditions as for the previous example) retention time 17.92 minutes; mass spectroscopy, m/e (positive electrospray ($ES^+$) 809.6 ($MH^+$).

The starting material was prepared as follows:

2-Propylpentanoyl-(D)Lys(BOC)-NMe(D)Phe-DTrp-OH was prepared by the same method as described in example 4, but on a smaller scale (0.33mmol). Yield 248mg (82%). RP-HPLC Vydac C18 column, 201HS54, 4.6x250mm, eluting with acetonitrile and water containing 0.1% TFA, using a 25-90% acetonitrile gradient over 40 minutes, flow rate 1.2ml/minute, retention time 18 minutes, no detectable impurities.

**Example 7**



**4,5-Dimethoxy-2-nitrobenzoyl-NMeTrp-piperazine-4-nitrophenyl**

A portion of 4,5-dimethoxy-2-nitrobenzoyl-NMeTrp-OH (43mg, 0.1mmol) was coupled to 4-(nitrophenyl)piperazine (21mg, 0.1 mmol) in DMF (4ml) using diisopropylethylamine (80 microlitres, 4 equivalents) and HATU (38mg, 1mmol). The reaction was complete after 1 hour, as judged by HPLC. The solution was diluted with water (2ml), filtered and put directly on a Dynamax C18 preparative column and eluted with a gradient of acetonitrile - water containing 0.1% TFA (20-70% acetonitrile) over 70 minutes at a flow rate of 12ml/minute. Fractions which contained product (eluting at 65 minutes) were combined and freeze dried. Yield 32mg.

RP-HPLC retention time 19.83 minutes (column and conditions as for previous example); mass spectroscopy, m/e (negative electrospray ($ES^-$)) 615.4 ($MH^-$).

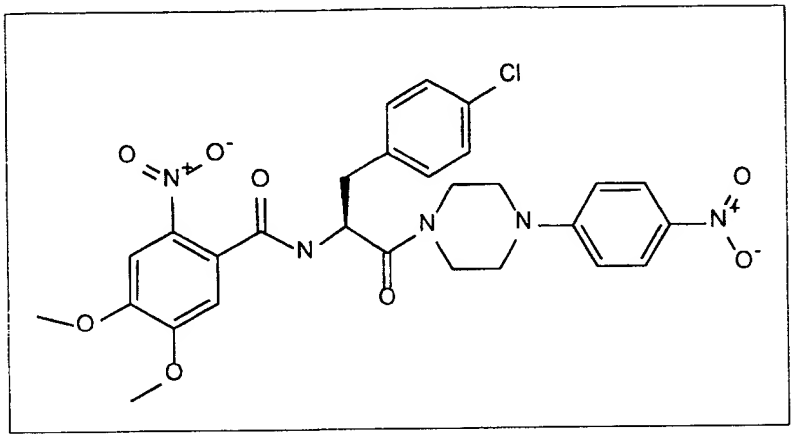
The starting material was prepared as follows:

4,5-Dimethoxy-2-nitrobenzoyl-NMeTrp-OH was prepared from 2-chlorotritylchloride resin (Alexis, 380mg, 0.5mmol) by the automated procedure described in example 4. After coupling Fmoc-NMeTrp-OH to the resin and subsequent Fmoc-deprotection, 4,5-dimethoxy-2-nitrobenzoic acid was coupled to the resin-bound NMethyl-Trp by the HATU procedure. The completed resin was collected and washed with methanol and dried at 50°. Yield 487mg (gain 107mg).

The 4,5-dimethoxy-2-nitrobenzoyl-NMeTrp-OH was cleaved from the resin with dichloromethane, trifluoroethanol and acetic acid as described previously. It was freeze-dried from water and acetonitrile. Yield 173mg (yellow powder) (82%) RP-HPLC at 50°C, Vydac

acetonitrile - water over 40 minutes, flow rate 1.3ml/minute, retention time 17.26 minutes, mass spectroscopy, m/e (negative electrospray ($ES^-$)) 425.6 ($MH^-$).

**Example 8**




**4,5-Dimethoxy-2-nitrobenzoyl-Phe(4-Cl)-piperazine-4-nitrophenyl**

This was prepared using a similar method to that of example 7. Preparative RP-HPLC was performed using a gradient 20-80% acetonitrile, 0.1% TFA over 70 minutes. Fractions which contained the title product (eluting at 59 minutes) were pooled and freeze-dried. Yield 40mg.

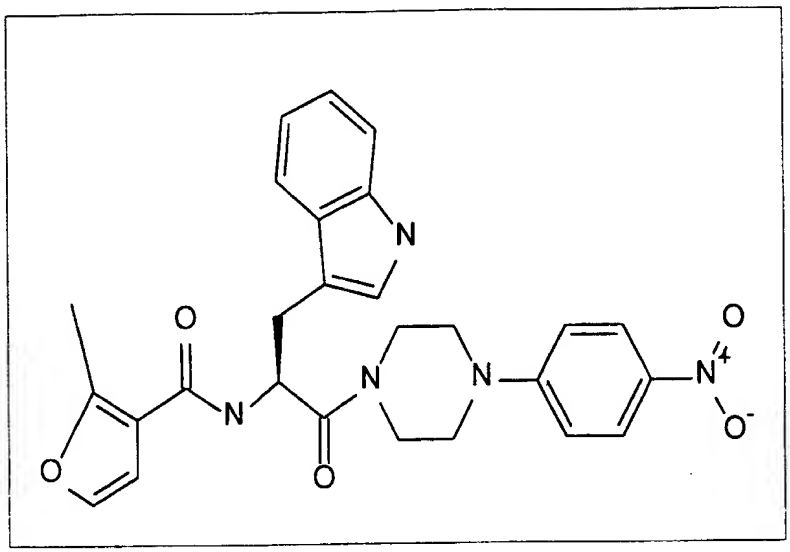
RP-HPLC column and element as for previous example, except that gradient 10-70% acetonitrile over 30 minutes, retention time 20.81 minutes; mass spectroscopy, m/e (negative electrospray ($ES^-$) 596.3 ($MH^-$).

The starting material was prepared as follows:

4,5-Dimethoxy-2-nitrobenzoyl-Phe(4-Cl)-OH was prepared using a similar method to that of example 7. Yield 203mg (100%).

RP-HPLC Vydac C18 column, 201HS54 4.6x250mm, eluting with a gradient 10-70%, 0.1% TFA acetonitrile-water over 40 minutes, flow rate 1.2ml/minue, retention time 178.5 minutes.

**Example 9**



**2-Methyl-3-furoyl-Trp-piperazine-4-nitrophenyl**

The amminolysis of 2-methyl-3-furoyl-Trp-O-Kaiser's oxime resin was carried out at 80°C in trichloroethane for 2 hours with 1 equivalent of 4-nitrophenylpiperazine and acetic acid (1-2 molar). The mixture was filtered and the resin was washed repeatedly with dichloromethane. The combined filtrate and washings were evaporated to dryness and the residue was dissolved in water (4ml) and acetonitrile (4ml) for HPLC and LC-MS, then freeze dried. Yield 29.8mg.

RP-HPLC column and elements as for previous examples, gradient 5-70%, 0.1% TFA acetonitrile -water over 40 minutes, flow 1.2ml/minute. Indicated that main peak (retention time 25.5 minutes) was expected product, (65.7% by peak integration at 230nm). LC MS $MH^+$ for main peak 502.3 (calc 501.55 mw).

The starting material was prepared as follows:

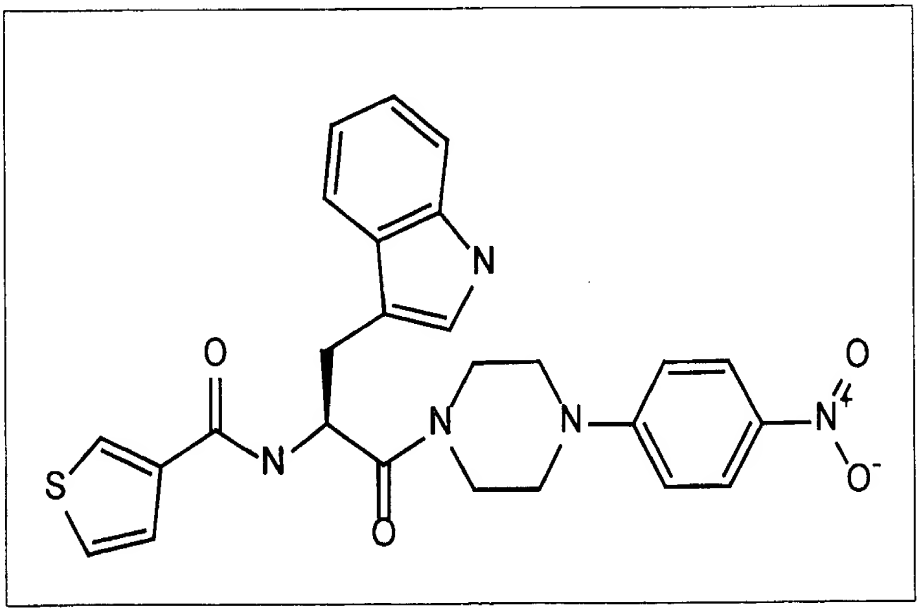
BOC-Trp-OH (4.6g, 15 mmol) was dissolved in dichloromethane (30ml) containing DMF (3ml) and diisopropylcarbodiimide (0.95g, 7.5mmol) was added. After 20 minutes at ambient temperature, the solution of preformed symmetrical anhydride was added to a bond-elute tube (80ml) containing Kaiser's oxime resin (5g, 1.21 mmol/g, 6mmol), which was already swollen in dichloromethane. After manual mixing for 5 minutes, dimethylamino pyridine (92mg, 0.75 mmol) was added and mixing continued at intervals over 2 hours. The resin was filtered and washed repeatedly with dichloromethane. Unreacted sites on the resin were then "capped" with 2,6-dichlorobenzoylchloride (0.63g, 3mmol) in dichloromethane

(30ml). After 1 hour at ambient temperature, the resin was filtered and washed with dichloromethane.

Deprotection was performed with 25% TFA in dichloromethane containing triisopropylsilane (5%). Three separate treatments carried out for 10 minutes each to ensure complete removal of BOC group. After extensive washing with dichloromethane to ensure most of the surplus TFA had been removed, the resin was divided into roughly equal portions, into 50 bond elute tubes (3ml) to give 0.12 mmol of TFA salt of Trp-O-oxime resin per tube.

To one of these portions of loaded resin, was added 2-methyl-3-furoic acid (64mg, 0.5mmol) dissolved in a solution of HBTU in DMF (0.33M, 1.5ml, 1 equivalent), followed after brief mixing, by isopropylethylamine (263 microlitre, 1.5mmol). After 5 hours at ambient temperature, the resin was filtered and washed with DMF to afford 2-methyl-3-furoyl-Trp-O-oxime resin.

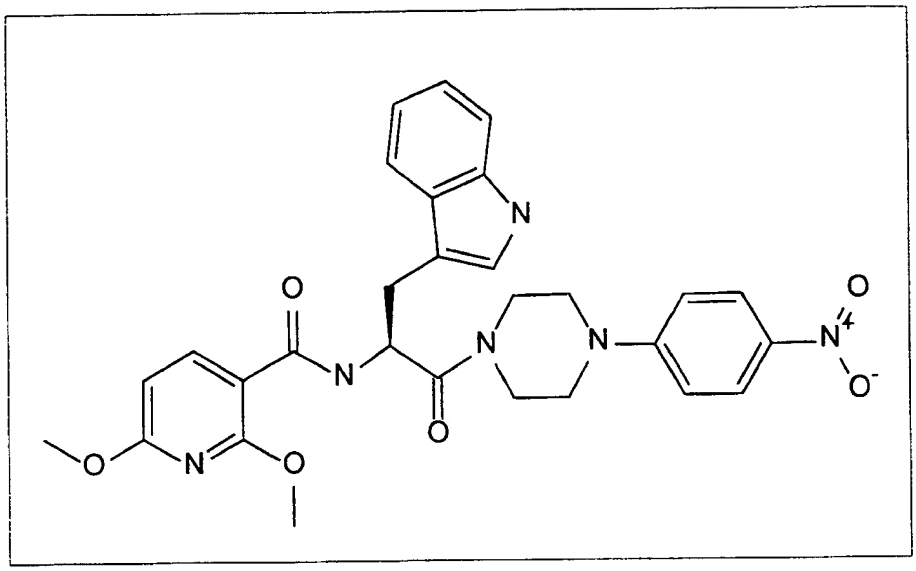
**Example 10**




**Thien-3-ylcarbonyl-Trp-piperazine-4-nitrophenyl**

The title compound was prepared by substitution of thiophene-3-carboxylic acid for the furoic acid in example 9, and the title compound was obtained by freeze drying. Yield

**Example 11**



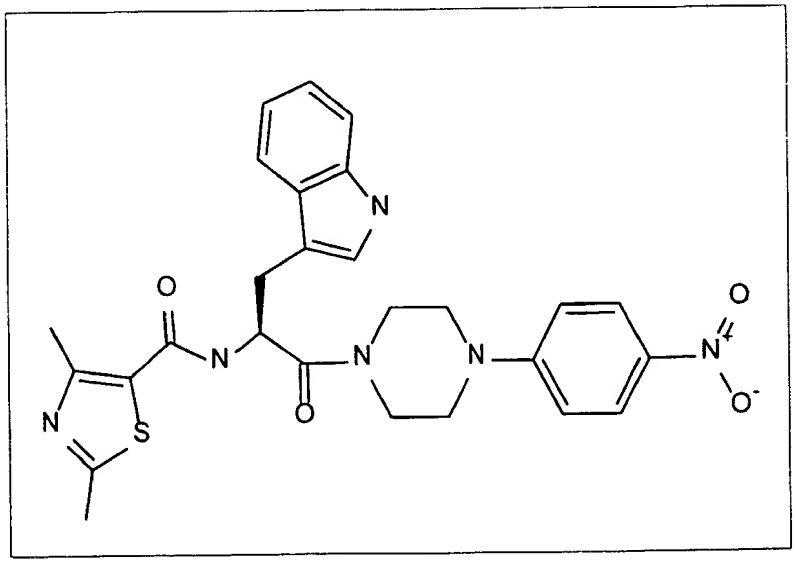
**2,6-Dimethoxynicotinoyl-Trp-piperazine-4-nitrophenyl**

The title compound was prepared by substitution of 2,6-dimethoxynicotinic acid for the furoic acid in example 9. Yield 39.5mg.

RP-HPLC column and conditions as described in examples above.

Retention time 27.9 minutes, 78% by peak integration at 230nm. LC MS $MH^+$ for main peak 559.6.

**Example 12**



**2,4-Dimethylthiazol-5-ylcarbonyl-(L)-Trp-4-piperazine-4-nitrophenyl**

This preparation was performed as part of a run on the Abimed AMS432 multiple parallel peptide synthesiser (MPPS) synthesiser:

BOC-(L)-Trp-oxime resin (100mg 110μmol) (prepared as in example 9) was placed in a reactor (8ml Bond-Elut). The instrument had been programmed to swell the resin by rinsing with dichloromethane. The resin was next treated 4 x 10 minutes with 25% TFA in dichloromethane which removes the BOC group. The resin was rinsed 6 times for 1 minute with dichloromethane, followed by 6 rinses for 1 minute with DMF. 2,4-Dimethylthiazole-5-carboxylic acid DIPEA (1000 μl of 0.5M) in NMP (1.0M ) and HBTU in NMP (1100μl 0.45M) were added to the resin. The mixture was stirred briefly by hand then allowed to proceed for 1hour. The reaction mixture was drained and the resin rinsed 6 times with DMF and 3 times with dichloromethane and allowed to air dry to give 2,4-dimethylthiazole-5-carbonyl-(L)-Trp-oxime resin.

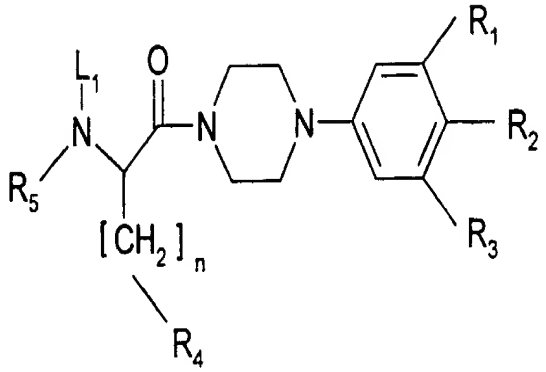
The resin was transferred to a sealed reaction vessel and suspended in TCE (2ml) . The suspension was treated with 1ml of a solution containing N-(4-nitrophenyl)-piperazine (100 μmol) and glacial acetic acid (400 μmol). The reaction vessel was sealed then left overnight in an oven at 75-80°C. After the overnight reaction, the reaction mixture was filtered, the residual resin was rinsed 4 times with DMSO (0.5ml). The combined filtrates were evaporated to dryness on a centrifugal evaporator and the residue was re-dissolved in DMSO (5ml ca 20mM solution). The solution was stored frozen at -20°C.

A sample of the solution was diluted 50 times with water to provide a sample for LC-MS analysis:

Theory $mH^+ = 533.6$ Found $mH^+ = 533.1$

## CLAIMS

1. A compound of formula (1):



formula (1)

wherein :

$L_1$ is hydrogen or methyl;

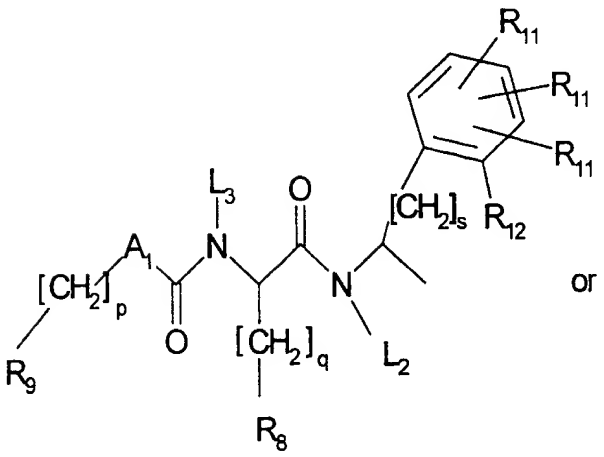
$R_1$ and $R_2$ and $R_3$ are each independently hydrogen, halo, nitro, cyano, carbamoyl, N-($C_{1-4}$alkyl)carbamoyl, NN-(di$C_{1-4}$alkyl)carbamoyl or $C_{1-4}$alkoxycarbonyl;

$R_4$ is indole, N-($C_{1-4}$ alkyl) indole, $C_{5-7}$carbocyclic ring or aryl, any of which can be optionally substituted on ring carbon atoms with up to three substituents each independently selected from halo, $C_{1-4}$alkyl, or $C_{1-4}$alkoxy;

$R_5$ is hydrogen, $C_{1-4}$alkyl, $R_6CH_2-$ or $R_6C(O)-$;

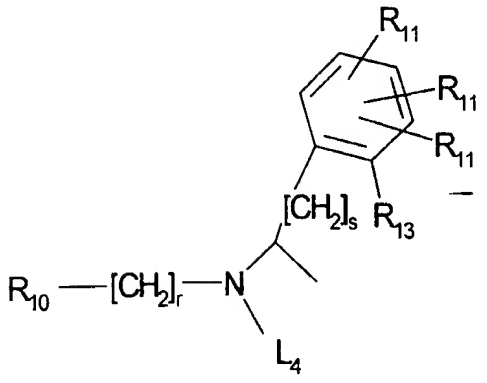
$R_6$ is aryl, heteroaryl, heterocyclyl, amino$C_{3-6}$alkyl, N-($C_{1-4}$alkyl)amino$C_{3-6}$alkyl, NN-(di$C_{1-4}$alkyl)amino$C_{3-6}$alkyl, or $R_7$; wherein the aryl, heteroaryl or heterocyclyl rings may be optionally substituted with up to three substituents independently selected from nitro, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, halo, ($C_{1-4}$alkyl)sulfanyl,

wherein $R_7$ is either a group of formula (2) of formula (3):



Formula (2)

or



Formula (3)

wherein:

$L_2$, $L_3$ and $L_4$ are each independently hydrogen or methyl;

$R_8$ is amino, guanadino, imidazolo, any of which can be mono or di-N-substituted with $C_{1-4}$alkyl;

$A_1$ is oxygen or a direct bond;

$R_9$ is a $C_{5-8}$ membered mono-carbocyclic ring, a $C_{6-10}$ membered bi-carbocyclic ring, $C_{8-12}$ membered tri-carbocyclic ring, $C_{5-7}$alkyl or aryl, any of which can be optionally mono, bi or tri substituted by $C_{1-4}$ alkyl;

$R_{10}$ is $C_{1-6}$alkyl or a $C_{3-8}$mono-carbocyclic ring;

$R_{11}$ is hydrogen, halo, $C_{1-4}$alkyl, or $C_{1-4}$alkoxy;

$R_{12}$ is hydrogen or methyl or ethyl or $R_{12}$ together with $L_2$ forms a $C_{5-7}$ nitrogen-containing heterocyclic ring;

$R_{13}$ is hydrogen or methyl ethyl or $R_{13}$ together with $L_4$ forms a $C_{5-7}$ nitrogen-containing heterocyclic ring;

n is 0, 1 or 2;

p is 0, 1 or 2;

q is an integer from 1 to 6

r is 0, 1 or 2;

provided that when $R_6$ is aryl, heteroaryl, heterocyclyl, amino$C_{3-6}$alkyl, N-($C_{1-4}$alkyl)amino$C_{3-6}$alkyl or NN-(di$C_{1-4}$alkyl)amino$C_{3-6}$alkyl then $R_5$ is other than $R_6CH_2$—; and when $R_1$ to $R_3$ are each hydrogen, $L_1$ is hydrogen, n is1, $R_4$ is phenyl, $R_5$ is $R_6C(O)$—, then $R_6$ cannot be 2-methyl-4-amino-butyl,

or a pharmaceutically acceptable salt, prodrug or solvate thereof.

2. A compound according to claim 1 wherein $R_5$ is hydrogen.

3 A compound according to claim 2 wherein $R_1$ is hydrogen; $R_2$ is nitro; $R_3$ is hydrogen; n is 1; $R_4$ is indole, N-($C_{1-4}$ alkyl)indole, cyclohexyl or phenyl any of which can be optionally substituted on ring carbon atoms with up to three substituents each independently selected from halo, $C_{1-4}$alkyl, or $C_{1-4}$alkoxy, $L_1$ is hydrogen and $R_5$ is hydrogen.

4. A compound according to claim 1 wherein $R_5$ is $R_6C(O)$—; $R_6$ is aryl, heteroaryl, heterocyclyl, amino$C_{3-6}$alkyl, N-($C_{1-4}$alkyl)amino$C_{3-6}$alkyl, or NN-(di$C_{1-4}$alkyl)amino$C_{3-6}$alkyl, wherein the aryl, heteroaryl or heterocyclyl rings can be optionally substituted on ring carbon atoms with up to three substituents each independently selected from nitro, halo, $C_{1-4}$alkyl, or $C_{1-4}$alkoxy.

5. A compound according to claim 4 wherein $R_1$ is hydrogen; $R_2$ is nitro; $R_3$ is hydrogen; n is 1; $L_1$ is hydrogen; and $R_6$ is aryl or heteroaryl wherein the aryl or heteroaryl can be

8. A compound according to claim 7 wherein $R_1$ is hydrogen; $R_2$ is nitro; $R_3$ is hydrogen; n is 1; $L_1$ is hydrogen; $L_2$ is hydrogen or methyl; q is an integer between 2 and 4; $R_8$ is amino; s is 1 and $L_3$ is hydrogen or methyl.

9. A compound according to claim 6 wherein $R_7$ is of Formula (3).

10. A compound according to claim 9 wherein $R_1$ is hydrogen; $R_2$ is nitro; $R_3$ is hydrogen; n is 1; s is 1 and $L_1$ is hydrogen,

11. A compound selected from the following:

4,5-dimethoxy-2-nitrobenzoyl-PHE(4-Cl)-piperazine-4-nitrophenyl;

4,5-dimethoxy-2-nitrobenzoyl-NMe-TRP-piperazine-4-nitrophenyl;

4,5-dimethoxy-2-nitrobenzoyl-(D)($N^{in}$-Me)TRP-piperazine-4-nitrophenyl;

Z-(D)(NMe)DAB-(NMe)(D)PHE-(D)TRP-piperazine-4-nitrophenyl;

Z-NMe(D)LYS-NMe(D)PHE-(D)PHE(4-Cl)-piperazine-4-nitrophenyl;

cyclohexyl-CO-(D)LYS-(D)NMe-PHE-CHA-piperazine-4-nitrophenyl;

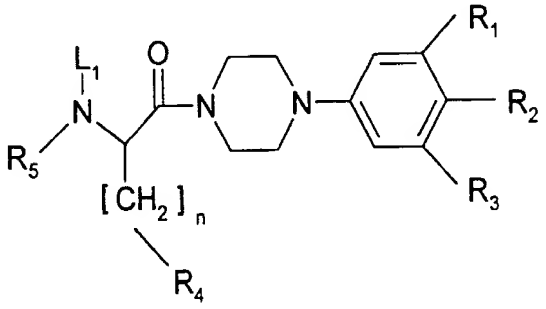
cyclohexyl-(D)Lys-(D)(NMe)Phe-(D)Phe(4-Cl)-piperazine-4-nitrophenyl;

cyclohexyl-$CH_2$-(D,L)NMe-PHE{$CH_2NH$}(D)TRP-piperazine-4-nitrophenyl; and

cyclohexyl-(D)Lys-(D)(NMe)Phe-(D)hPhe-piperazine-4-nitrophenyl;

or a pharmaceutically acceptable salt, prodrug or solvate thereof.

14. The use of a compound of Formula (4) in the manufacture of a medicament for the treatment of cancer in a warm-blooded animal.



formula (4)

wherein :

$L_1$ is hydrogen or methyl;

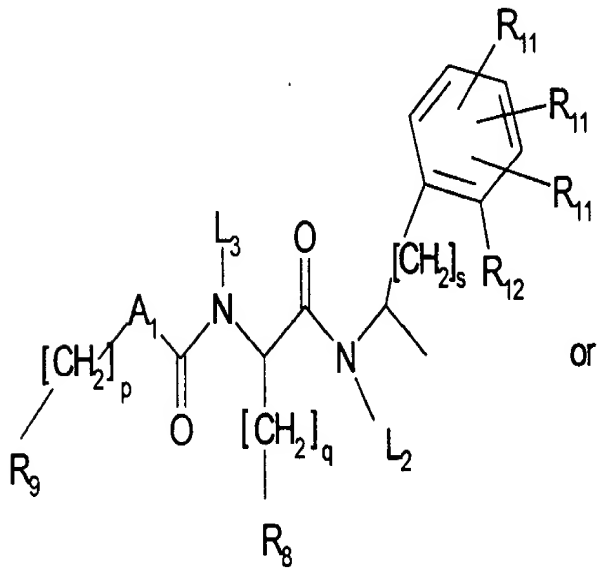
$R_1$ and $R_2$ and $R_3$ are each independently hydrogen, halo, nitro, cyano, carbamoyl, N-($C_{1-4}$alkyl)carbamoyl, NN-(di$C_{1-4}$alkyl)carbamoyl or $C_{1-4}$alkoxycarbonyl;

$R_4$ is indole, N-($C_{1-4}$ alkyl) indole, $C_{5-7}$carbocyclic ring or aryl, any of which can be optionally substituted on ring carbon atoms with up to three substituents each independently selected from halo, $C_{1-4}$alkyl, or $C_{1-4}$alkoxy;

$R_5$ is hydrogen, $C_{1-4}$alkyl, $R_6CH_2-$ or $R_6C(O)-$;

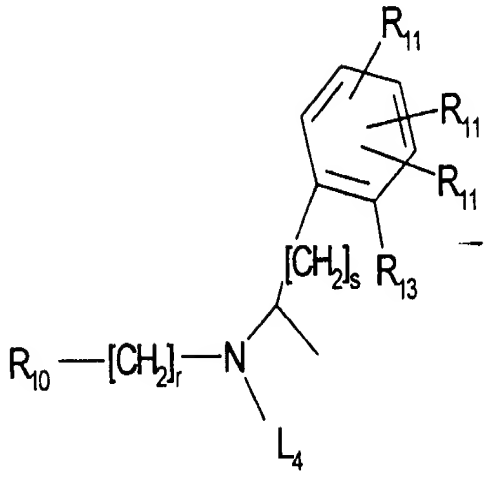
$R_6$ is aryl, heteroaryl, heterocyclyl, amino$C_{3-6}$alkyl, N-($C_{1-4}$alkyl)amino$C_{3-6}$alkyl, NN-(di$C_{1-4}$alkyl)amino$C_{3-6}$alkyl, or $R_7$; wherein the aryl, heteroaryl or heterocyclyl rings may be optionally substituted with up to three substituents independently selected from nitro, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, halo, ($C_{1-4}$alkyl)sulfanyl, $C_{1-4}$ alkoxycarbonyl, N-($C_{1-4}$ alkyl)carbamoyl, NN-(di$C_{1-4}$ alkyl)carbamoyl, N-($C_{1-4}$ alkyl)amino or NN-(di$C_{1-4}$ alkyl)amino;

wherein $R_7$ is either a group of formula (5) of formula (6):



Formula (5)

or



Formula (6)

wherein:

$L_2$, $L_3$ and $L_4$ are each independently hydrogen or methyl;

$R_8$ is amino, guanadino, imidazolo, any of which can be mono or di-N-substituted with $C_{1-4}$alkyl;

$A_1$ is oxygen or a direct bond;

$R_9$ is a $C_{5-8}$ membered mono-carbocyclic ring, a $C_{6-10}$ membered bi-carbocyclic ring, $C_{8-12}$ membered tri-carbocyclic ring, $C_{5-7}$alkyl or aryl, any of which can be optionally mono, bi or tri substituted by $C_{1-4}$ alkyl;

$R_{10}$ is $C_{1-6}$alkyl or a $C_{3-8}$mono-carbocyclic ring;

$R_{11}$ is hydrogen, halo, $C_{1-4}$alkyl, or $C_{1-4}$alkoxy;

$R_{12}$ is hydrogen or methyl or ethyl or $R_{12}$ together with $L_2$ forms a $C_{5-7}$ nitrogen-containing heterocyclic ring;

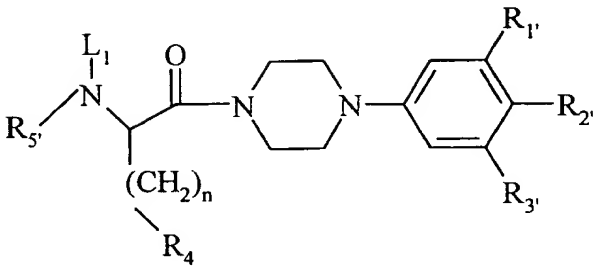
provided that when $R_6$ is aryl, heteroaryl, heterocyclyl, amino$C_{3-6}$alkyl, N-($C_{1-4}$alkyl)amino$C_{3-6}$alkyl or NN-(di$C_{1-4}$alkyl)amino$C_{3-6}$alkyl then $R_5$ is other than $R_6CH_2$–; or a pharmaceutically acceptable salt, prodrug or solvate thereof.

15. A method of treating cancers which comprises administering to a warm-blooded animal an effective amount of a compound of formula (4).

16. A pharmaceutical composition comprising a compound of formula (4), or a pharmaceutically acceptable salt, prodrug or solvate thereof , in admixture with a pharmaceutically-acceptable diluent or carrier for the treatment of cancer in a warm-blooded animal.

17. A process for preparing a compound of the formula (1) or a pharmaceutically acceptable salt, prodrug or solvate thereof which process comprises:

a) reacting a carboxylic acid of Formula (8) or a reactive derivative thereof with a piperazine of formula (9)



Formula (7)

b) removing any protecting groups,

c) optionally forming a pharmaceutically acceptable salt, prodrug or solvate.

# INTERNATIONAL SEARCH REPORT

[redacted] onal Application No
PCT/GB 99/02957

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K5/08 C07D295/185 C07D209/20 A61K38/06 A61K31/495
A61K31/496 C07D405/12 C07D409/12 C07D401/12 C07D417/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | CHEMICAL ABSTRACTS, vol. 116, no. 13, 30 March 1992 (1992-03-30) Columbus, Ohio, US; abstract no. 128656z, FURUTA TAKUYA ET AL.: "Preparation of Indole Derivatives as Vasopressin Antagonists" page 863; column 1; XP002125251 abstract -& CHEMICAL ABSTRACTS 13TH COLLECTIVE INDEX; CHEMICAL SUBSTANCES (AZAU...-BENZAMIDE, TETRAE...), vol. 116-125, 1992 - 1996, page 1647 XP002125250 Columbus, Ohio, US column 2, line 60 - line 64 & JP 03 127732 A (OTSUKA PHARMACEUTICAL) 30 May 1991 (1991-05-30) -/-- | 1,4,12, 17 |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 20 December 1999 | 19/01/2000 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040. Tx. 31 651 epo nl, Fax: (+31-70) 340-3016 | Zervas, B |

Form PCT/ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

[redacted] onal Application No
PCT/GB 99/02957

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No |
|---|---|---|
| A | WO 98 01467 A (NOVARTIS)<br>15 January 1998 (1998-01-15)<br>cited in the application<br>claims; examples | 1,12,14,<br>16 |

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

national application No.
PCT/GB 99/02957

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 13, 15
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 13 and 15 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

[redacted]ation on patent family members

[redacted]onal Application No
PCT/GB 99/02957

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 9801467 A | 15-01-1998 | AU 3847997 A | 02-02-1998 |
| | | CA 2259149 A | 15-01-1998 |
| | | EP 0958305 A | 24-11-1999 |